# SPEECH DISORDERS
# AND
# LESIONS OF THE BASAL GANGLIA

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C.V.GAMSU

DOCTOR OF PHILOSOPHY
UNIVERSITY OF EDINBURGH
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I hereby declare that

I have composed this thesis myself

and that the work here reported is my own.

## SUMMARY

This research project was designed to investigate the nature of the speech disorders consequent upon lesions of the basal ganglia. For many years it was assumed that the speech disorders associated with basal ganglia damage were no more than a manifestation of underlying rigidity. However, experience has shown that surgery which successfully ameliorates the rigidity in no way lessens the speech disturbance of patients with Parkinson's disease. Indeed, in some studies, there are reports of speech disturbances being induced by the operation.

From the literature, it seems that there is a strong case for the assumption that the speech disturbances are due not to rigidity, but to akinesia. This project was designed to test this hypothesis.

The background literature upon which the hypothesis is based is reviewed in the first four chapters of this thesis. Chapter 5 describes the experimental design (in which dopamine - an amine implicated in akinesia was used as an experimental variable); the experimental group (a series of patients with either paralysis agitans or post-encephalitic Parkinsonism. The group included some patients who had previously undergone stereotactic surgery);and the tests and tasks set the subjects.

The results of the investigation are presented in Chapter 6 to 9. These results are evaluated in Chapter 10. In brief, it may be said that the results vindicate the hypothesis of the investigation. This chapter also includes a consideration of the clinical and theoretical implications of the findings.

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# INTRODUCTION

It is only in the past decade that the nuclei of grey matter situated deep within the cerebral hemispheres, the 'basal ganglia', have become amenable to serious investigation. Before the advent of stereotactic surgery, and before the important, recent, developments in biochemistry of the brain, the function of these ganglia could be postulated only on the basis of clinical observation.

Lesions of the basal ganglia dramatically disturb motor function and in the past it was to this aspect that attention was directed. However, lesions of the basal ganglia also disturb speech. Patients with Parkinson's disease or with Wilson's disease, or with diseases which fall within the category of 'hyperkinetic' motor disturbances (such as athetosis) frequently exhibit disordered speech.

It is tempting to dismiss these speech disturbances as being no more than a special case of the more general motor disturbance. But the relationship between speech and motor disturbance is not really so simple or clear cut. The one disturbance may be exhibited in the absence of the other. When they do occur together, medication

"has often improved gross motor functions but has not usually been effective in improving speech" (Canter, 1961). Stereotactic surgery, too, has a differential effect. It alleviates, often spectacularly, tremor and rigidity, but all too frequently it has the unfortunate side-effect of exacerbating existing speech disorders, and, in some cases with previously unimpaired speech, of *inducing* not only the speech but also language disturbances (see, for example, Cooper, 1961; Allan et al., 1966; and Hermann et al., 1966).

The nature of the relationship between speech and the basal ganglia is not readily apparent. Hughlings Jackson (1866) touched briefly on the subject and provided a simple rule-of-thumb: "I think it will be found that the nearer the disease is to the corpus striatum, the more likely is the defect of articulation to be the striking thing, and the farther off, the more likely it is to be one of the mistakes of words". The French neurologist Pierre Marie considered the subject to be far more complex than other neurologists of the time would concede. For Marie language and speech could not so readily be considered discrete; their area of overlap was well demonstrated in that disorder referred to by a variety of names - 'Broca's aphasia', 'motor aphasia', 'cortical dysarthria', or, in Marie's own terminology, 'anarthria'. Working from the premise that the basal ganglia are part of the effector mechanism whereby 'language' is manifest as 'speech', Marie insisted that damage to subcortical structures had

a more serious effect on communication skills than the mere production of "simple dysarthria". (See Chapter 4 for a full discussion of these theories).

Unfortunately, differences of opinion as to the nature of the role played by subcortical mechanisms in communication are not solely a philosophical problem. As the recent experience of serious impairment to communication resulting from stereotactically-induced pallidal and thalamic lesions has proved, both from a clinical and from a theoretical standpoint, the question of speech disorders and lesions of the basal ganglia can no longer be ignored.

The experimental work reported in this thesis is based on a group of patients with either Parkinson's disease or post-encephalitic Parkinsonism. This group of patients were selected for a number of reasons. The Parkinsonian syndrome is today considered "the most characteristic or most representative" of diseases involving lesions of the basal ganglia (DeJong, 1967); it is also one of the more common subcortical diseases. A new approach to the treatment of Parkinsonism, based on recent advances in biochemistry, promises the possibility of being able for the first time to ameliorate not only gross motor, but also speech disturbances.

# CHAPTER 1

# PARKINSON'S DISEASE AND THE PARKINSONIAN SYNDROME

## HISTORY OF THE SYNDROME

> Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from walking to a running pace: the senses and intellect being uninjured.
>
> *James Parkinson, 1817.*

In 1817, James Parkinson, a London physician, published a slim monograph describing, for the first time, a disease that had "not yet obtained a place in the classification of nosologists". In 1955, a bicentenary volume of papers dealing with Parkinson's disease was published. In it, Francis Walshe reflected on the value and merit of Parkinson's work:

> It was his discernment of the slow unfolding of a constant pattern of symptoms that enabled Parkinson to pick out the malady now commonly named after him from the clinically undifferentiated mass of illness in which tremor was a presenting symptom; and though succeeding generations of nosographers have added further items of the visible as well as of the palpable to the syndrome thus so succinctly described, Parkinson's account remains remarkable for what it contained and for its clarity and conciseness.

Parkinson referred to his disease by two names, 'shaking palsy' and paralysis agitans'. The latter

seems to have gained almost instant popularity (see, for example, Cooke, 1823). Today the term 'paralysis agitans' and the eponym, 'Parkinson's disease', introduced by Charcot, are used interchangeably.

The monograph, *An Essay on the Shaking Palsy*, began with the now-famous clinical definition quoted above. As Parkinson so clearly stated, the disease is essentially one involving motor dysfunction. It is characterized by a 'triad' of motor symptoms: rigidity, tremor, and loss of associated and automatic movements (Souques, 1921). It is a progressive disease, and affects adults in the second half of life. The cause of the disease is still unknown. Its incidence is large, with a prevalence of approximately 1 in every 1,000 of the population. Apart from vascular disease, Parkinson's disease and the Parkinsonian syndrome may be considered the commonest disabling disease of the nervous system.

Apart from this idiopathic form described by Parkinson, there are several 'secondary' forms of the disease. The first of these forms to be described in medical literature emerged during the last years of the First World War, in a series of epidemics.

Von Economo, in May 1917, published a report on an epidemic in Vienna of what he termed 'encephalitis lethargica'. The epidemic, however, was also much in evidence throughout France (Cruchet et al., 1917), and Britain. By the 1920's, it was found in other parts of Europe (the Netherlands, Germany, Warsaw, Italy, Sweden,

the Ukraine and Switzerland) and in other parts of the world (Algiers and South Africa, North America, India, the Phillippines, and Guatemala) (Hall, 1924). Although the disease itself was not new, these epidemics differed sufficiently from previous outbreaks of encephalitis to prompt Arthur Hall, and other neurologists, to conclude that this particular epidemic was "something *sui generis*". Not only did the extent and severity of this particular outbreak of encephalitis set it apart from previous epidemics, but the 'residua' evident either immediately, or some time, after the acute phase of the disease had passed, had new and unprecedented aspects. As Hall explained:

> Epidemic encephalitis has established itself as a separate disease chiefly by the number and the peculiarity of its later manifestations. "By their fruits ye shall know them" is indeed applicable to this disease.
>
> Of the late manifestations or residua, perhaps the most frequent and certainly the most unexpected, is that strange clinical picture the resemblance of which to paralysis agitans of advanced years is in some respects so close. To this 'post-encephalitic' group of symptoms the term 'Parkinsonian syndrome' or 'Parkinsonism' has been given by the French School.

In one of the earlier surveys, it was estimated that 25% of 'fully developed' cases of epidemic encephalitis had as a consequence some form of Parkinsonism. However, by 1922, Goldflam said of the epidemic at Warsaw in 1920, "We may almost speak of an epidemic of paralysis agitans". Hall (1924) concurred: his figures suggested that, if not all, then an extremely large proportion of the 'fully developed' cases who survived exhibited Parkinsonian residua. As is to be expected, since

encephalitis is not restricted to any particular age-group, post-encephalitic Parkinsonism, unlike paralysis agitans, is found across an extremely large age-range of patients.

In 1929, Critchley argued the case for yet another 'secondary' form of Parkinsonism - arteriosclerotic Parkinsonism. In his article he admitted that a definition of this syndrome was not possible, but he listed the points of clinical distinction between arteriosclerotic Parkinsonism and Parkinson's disease. He paid particular attention to the pathological changes that distinguish the two, and which are revealed on post mortem. It is only on the basis of post mortem examination that an unequivocal diagnosis of arteriosclerotic Parkinsonism can be made. A provisional diagnosis on history and symptomatology, however, may sometimes be made. Symptoms of arteriosclerotic Parkinsonism usually appear after the age of sixty; tremor is mild or absent and often the patient shows psychological signs of organic brain disease not commonly associated with idiopathic or post-encephalitic Parkinsonism.

'Secondary', or 'symptomatic' Parkinsonism has also been attributed, but far more rarely, to toxic substances (such as manganese, carbon monoxide), to biochemically active substances (such as reserpine, chlorpromazine), and to trauma (usually repeated minor forms, such as boxing). It may also, occasionally, be associated with

degenerative neurological disorders of unknown aetiology (such as Creutzfeldt-Jakob disease) and with others (such as syphilis). The association between Creutzfeldt-Jakob disease and Parkinson's disease is particularly interesting in the light of a recent report that Creutzfeldt-Jakob disease is transmittable to a lower species, such as the chimpanzee (Mathews et al., 1969). This indicates that Creutzfeldt-Jakob disease is one of the 'slow virus' diseases, and since it is (occasionally) associated with Parkinson's disease, there is some ground for the question: Is Parkinson's disease itself not one of the 'slow virus' diseases?

It is debatable whether or not paralysis agitans and the various "secondary" forms of Parkinsonism are indeed one syndrome. Houston Merritt (1954) believed "the symptom-complex identified by Parkinson stems from a variety of causes", and Critchley (1929) extended this proposition, claiming that the features which make up the Parkinsonian syndrome may have many different pathological causes but that the site of the pathology is always the same. Juxtaposing Gower's view (1910) on this topic highlights one of the aspects to be explained by advocates of such a null-hypothesis: "It is curious that the poisons which cause tremor do not cause paralysis agitans".

Walshe (1955), on the other hand, was adamant in his opposition to the 'one-syndrome' approach. He firmly believed "that Parkinson's shaking palsy is not precisely

the same sequence of events, or at any given time the same picture, as that presented by what we call post-encephalitic Parkinsonism. Still more clearly does it differ from the so-called arteriosclerotic Parkinsonism". Furthermore, he maintained: "To ignore these differences in the interests of what is a false simplicity is not to make useful generalizations, but to blur the fine points of clinical discrimination and to regress to a lower level of observational precision".

The experimental work reported herein is based on an acceptance of the premise that the various forms of Parkinsonism are sufficiently different to warrant treatment as entities in their own right. There is growing evidence to support this. For example, post mortem histological analysis shows qualitative differences between paralysis agitans and post-encephalitic Parkinsonism (see Chapter 3); paralysis agitans and the various 'secondary' forms of Parkinsonism respond differently to medication. Even among the smaller subset of 'secondary' Parkinsonian patients there is no universal form of treatment - syphilitic Parkinsonism responds (albeit occasionally) to penicillin, and drug-induced Parkinsonism to withdrawal of the offending substance.

Unfortunately, firm diagnosis of which type of Parkinsonism a particular patient is suffering from is not always easy. It is the patient with no significant diagnostic facts in his medical history, presenting at

an early age with Parkinsonian symptoms, who is difficult to categorize. Walshe (1955), perhaps a trifle long-windedly, explained the problem:

> ...for there can be no doubt that at this time the diagnostician faced by an example of Parkinsonism makes his choice between these two aetiologies: the post-infective and the degenerative, not on the signs alone, certainly not on the history which may be innocent of aetiological pointers, but on the patient's age at onset of the illness. If the patient be young, the tendency is to label the syndrome as post-encephalitic almost as a matter of course, despite the absence of any indication of an attack of epidemic encephalitis in the past. This view is based on the assumption - not justified - that juvenile or early adult paralysis agitans does not occur, or at least is so rare as not to demand consideration.
>
> My impression is that amongst the cases of the pure paralysis agitans syndrome, as I shall call it, that I have seen of late years, there is a larger proportion of patients in whom the onset dates from the thirties and the forties of life than was formerly the case.
>
> Used as we are to thinking of paralysis agitans as a degenerative or involutional disease, we tend without due grounds to regard these younger cases as post-encephalitic in origin: not considering that over the years the picture of disease and its age incidence may show changes that do not call for the invoking of new and special aetiologies.
>
> It may be that in our time paralysis agitans is showing a tendency to earlier appearance, and if this be a speculation as yet unproved, it is surely not more so than the bland general assumption that all cases of the paralysis agitans syndrome developing in early life or early adult life are encephalitic in origin.

In the categorization of patients in this investigation, the bias has been to diagnose as post-encephalitic only those patients with the characteristic history and compatible clinical picture. When this was in doubt, patients were considered to be of the paralysis agitans type. The speech of paralysis agitans patients is generally considered, on clinical evidence, to be less disturbed than the speech of post-encephalitic patients. Weighting the design of the investigation against this

popular belief was considered to be no disadvantage. Identifying the arteriosclerotic patient is , however, a somewhat different and difficult task, for arteriosclerotic changes are part of the normal ageing process. The clinical distinction between an idiopathic and an arteriosclerotic aetiology is frequently doubtful and made upon the basis of probabilities rather than any distinctive clinical features. Although for the purposes of this investigation patients with any of the following features were considered as arteriosclerotic (and excluded), it is to be accepted that, given the present state of the art, screening methods do produce a small number of false-positives and false-negatives: hypertension, retinal vascular changes, dementia, 'strokes', pseudobulbar palsy and bilateral pyramidal signs.

## CLINICAL FEATURES

Although Parkinsonism has an insidious onset, and the disease is slowly progressive, a patient with even mild Parkinsonism of short duration does present a characteristic picture. His posture is one of slight flexion of the neck and a round-shouldered stance; his face is immobile and his skin may be rather less wrinkled than would be expected for someone of his age and it may be slightly seborrhoeic. His eyes may show slight

widening, his blinking rate may be reduced, and there usually is a distinct lack, or slowness, of the normal play of facial expression during conversation.

A reduction of associated movements is particularly characteristic in the early stages. The patient appears wooden; gestures using the hands are minimal and, when sitting in a chair, the patient is quite still, with none of the normal small changes of posture over time. The patient's walking may be slower, and his paces may tend to be shuffled.

As the disease progresses, the intensity of the symptoms and signs of Parkinsonism increases. The symptom of primary interest here, that of disturbed speech, is discussed fully in Chapter 4. The present discussion is thus confined to the other major symptoms.

## TREMOR

The Parkinsonian tremor typically begins in one upper limb and later involves the lower limb on the same side. The contralateral limbs may be similarly affected after some time. The hand is the most affected, having a 'pill-rolling' movement. Small muscles, according to Wilson (1954), are particularly prone to show tremor, thus the muscle groups of the lips, tongue and larynx are frequently affected.

The rate of Parkinsonian tremor is between 4 and 8 oscillations a second. Brain (1964) believed the tremor of paralysis agitans to be slower than that of post-

encephalitic Parkinsonism. Tremor is typically present in paralysis agitans. It is less common in post-encephalitic Parkinsonism, and rare in all other varieties of 'secondary' Parkinsonism.

The tremor is evident when the affected limb is at rest but it disappears during sleep. Some patients notice moderate relief of mild tremor after drinking alcohol but this is never as dramatic as the relief alcohol produces in essential tremor. Conversely, Parkinsonian tremor is adversely affected by increases in intravenous adrenaline. Patients frequently report an increased intensity of tremor associated with strong emotional states. Noradrenaline, however, has no such effect.

## RIGIDITY

Rigidity is the second of the three cardinal features of the disease. Rigidity, that is the resistance felt by an examiner when a limb of the patient is passively moved, may classically be one of two types. The resistance may either be constant throughout the range of movement in whatever direction the examiner chooses ('lead pipe' rigidity) or it may have regular fluctuations of resistance ('cogwheel' rigidity).

Rigidity is generally first evident in the more proximal joints. It may be detectable in only one movement of one joint and is usually more easily demonstrable at the shoulder or elbow than in the

fingers. Disturbance of the respiratory muscles can often be demonstrated by a reduction in peak expiratory flow rate.

## AKINESIA

The third cardinal symptom of the disease, akinesia, is difficult to define. Unlike tremor, its presence is not self-evident, and unlike rigidity, it is not felt on examination of the patient. Instead its presence is inferred on observing that certain normal movements are delayed, slow and 'weak', and others are reduced in number or even absent. At its least powerful level, 'akinesia' may be considered an intervening variable to account for reduction or loss of movements. However, recent advances in biochemistry indicate that akinesia is more than an extremely useful hypothetical construct; akinesia is dependent upon and modifiable by certain biochemical agents (see Chapter 3). De Ajuriaguerra (1971) has suggested (but rejected, for obvious reasons) as a pragmatic, and simple, definition that "akinesia is what L-dopa modifies".

Over the years, a variety of terms and descriptive phrases have been used to refer to what is now called 'akinesia'. Parkinson described what he saw as a form of paralysis, "palsy", of gradual onset, that was never complete even in the advanced stages of the disease; it was always evident as an extreme slowness of movement. Souques (1921) who appears to be the first to have

referred to the 'triad' of Parkinsonian symptoms, wrote about "a loss of associated and automatic movement". Wilson (1925) originally used "akinesia" to describe "poverty or economy of movement".

The clinical picture presented by patients with marked akinesia, while being instantly recognizable, may vary from individual to individual. In the early stages, particularly where tremor is not the presenting symptom and rigidity is not felt, the akinetic picture is diagnostically important. The mask-like facies, with wide eyes, reduced blinking rate, slightly seborrhoeic, smooth skin is often seen. The patients appear to change facial expressions infrequently, and as Walshe (1955) pointed out, extremely slowly: "The immobile face ... can be made to show some natural play of expression: for example, if the patient be adequately amused he can smile again, though the movement of the smile is long drawn out, and hangs upon the face, as it were, almost like a posture".

Gait is frequently disturbed by akinesia. Parkinson considered this to be pathognomonic, and the second[1] cardinal feature of his disease. Patients may have difficulty in starting to walk. Once started, they may exhibit "a propensity ... to pass from walking to a running pace" (Parkinson, 1817). Parkinson noticed a similar disturbance to speech, i.e. uncontrolled

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[1]Tremor was the first; rigidity was not recognized by Parkinson

hastening, and used the term "festination" to describe both the speech and the gait disorder.

Movements of the upper limbs, either gestures in conversation, or arm-swinging in walking, tend to be minimal. Handwriting, and other tasks requiring a similar high degree of dexterity and fine manipulation are impaired. Patients frequently complain of 'weakness', not a true muscular weakness such as an inability to lift objects, but rather a weakness as after sustained activity or effort; a myasthenic weakness. Furthermore patients complain of 'slowing up', and are very much aware of how much longer than previously it takes them to dress, wash or feed.

## RESPIRATORY DISTURBANCES

Although Parkinson observed a patient who "fetched the breath rather hard", only four studies to date have considered the question of respiratory disturbance in Parkinsonism; the first of these were carried out in Germany by Schilling in 1925.

Schilling found that the rest breathing patterns of his patients (all had Parkinson's disease of recent onset) were markedly irregular, with long apneic periods between respiratory cycles. Cramer, in 1941, reported similar observations but on a group of six post-encephalitic Parkinsonian patients of long duration. She found, in addition, that their breathing was shallow, with little difference between the depth of quiet and

forced respiration. All her patients had rapid breathing rates, tremor of the respiratory muscles and seriously reduced vital capacities.

A more recent study, Nugent et al. (1958), however, failed to corroborate all of Cramer's findings. The respiratory characteristics of nine Parkinsonian patients who complained of dyspnoea on mild exertion were studied. Five cases were found to have greatly reduced maximum breathing capacities, but with only a mild reduction in vital capacity. Nugent and associates firmly believed that no "primary disease process other than the neurological disorder itself" could account for this respiratory insufficiency. However, although rigidity and 'weakness' of the thoracic musculature were suggested as possible causes, no definitive conclusions were reached concerning the physiological dysfunctions leading to the respiratory disturbances in these patients.

Two years later, in 1960, de la Torre and his co-workers reported the results of pulmonary function tests on twelve patients with various forms of Parkinsonism. Their results confirm Nugent's findings, and add an additional feature: the rest breathing patterns of the patients revealed obvious abnormalities of rate and depth. No correlation was found between clinical judgements of severity of rigidity of the trunk and the obtained respiratory measurements. The authors, therefore, suggest "incoordination of the respiratory musculature" might be responsible for both the

irregular rest breathing and the reduced maximum breathing capacities.

## MENTAL CHANGES

Parkinson was quite clear that in his disease "the senses and intellect [are] unimpaired". Dillar and Riklan (1956) empirically confirmed this, testing a large group of Parkinsonian patients on the Wechsler-Bellevue Scale. Nonetheless, they reported that a high percentage of their patients had psychological disturbances. Five per cent were diagnosed as schizophrenic; twenty-four per cent were described as "severely disturbed"; twelve per cent were shown to have organic brain syndromes, and only fifty-nine per cent were considered to be 'normal' with respect to psychological function. However, until we have a clearer understanding of how psychological functions are affected by a long, progressive illness, and by the experience of increasing dependency on others, it is perhaps rash and naïve to conclude that mental changes are essential features of Parkinsonism. As Noyes (1953) pointed out, in Parkinsonism, as in all chronic diseases, increased dependence may of itself create serious emotional problems. The suggestion by Laszewski (1956) that paranoid traits tend to occur in patients with severe tremor should, therefore, be regarded with scepticism. MacDonald Critchley (1955) in his introductory chapter to the bicentenary volume of papers on Parkinson and his work made a valid observation:

"Every physician knows that some of these Parkinsonian patients contrive to continue in business, industry, or in one of the trained professions, for a decade or more".

There are, in addition to the signs and symptoms already mentioned, other less striking yet highly characteristic symptoms of Parkinsonism. Blepharospasm, or involuntary tonic closure of the eyes, occurs particularly in post-encephalitic Parkinsonism. In idiopathic Parkinsonism there frequently is impairment of convergence. Excessive salivation is the most common autonomic abnormality in all forms of the disease. Seborrhoea, while common to all forms, is particularly evident amongst the post-encephalitic group. Postural hypotension is also seen, particularly in the akinetic patients. In the post-encephalitic patients oculogyric crises are evident.

## HISTORY OF TREATMENT

In spite of Parkinson's caution "until we are better informed respecting the nature of this disease the employment of internal medicines is scarcely warrantable", throughout the nineteenth century patients were subjected to a great variety of purgatives, salts of heavy metals, arsenic and alkaloids. Parkinson himself recommended blood-letting from the upper part of the neck

followed by "vesicatories to be applied to the same part". Ordenstein (1867), a student of Charcot, observed that belladonna alkaloids were beneficial, and for many years it was held that the Bulgarian extract of belladonna was superior to all others. Gowers (1910), although recommending hyoscyamus as an efficacious treatment, viewed the question of treatment with some despair: "but of all the degenerative diseases of the nervous system this is the least amenable to therapeutic agents and least capable of arrest". Belladonna and hyoscine, nevertheless, remained routine medication until 1945, when the synthetic compounds used today became available.

Of the synthetic anticholinergics, benzhexol, benztropine, procyclidine, ethopropazine, caramiphen and methixene are commonly used. "None of these", according to Mawdsley (1970), "is obviously better than the others and each physician tends to have his own list of favourites". Moreover,

> The principles of dosage are common to all these preparations. The drug is introduced in small amounts and gradually increased to the limit of tolerance. Dryness of the mouth and blurring of vision usually set the upper limit of dosage. The object is to achieve improvement without disabling side effects. If this be not possible with one drug, another attempt, using a different preparation, should be made. (Mawdsley, 1970)

Unfortunately, anticholinergic drugs have limited efficacy. The very large number of different preparations commercially available at present perhaps reflects the fact that the therapeutic response to these

drugs is often disappointing. It is the patient with mild symptoms (particularly mild rigidity) who shows greatest improvement with anticholinergic therapy. However, as the disease progresses, the effectiveness of all the anticholinergic preparations becomes less and the toxic effects more troublesome.

Mawdsley (1970) pointed out that another group of drugs, the antihistamines, have been used, and although they, too, have limited effect and tend to induce side-effects, thoughtful choice of treatment may turn these to use: "Diphenhydramine is helpful, but produces drowsiness, but sometimes this is helpful if the patient is already suffering from restlessness and excitement induced by an anticholinergic drug. Orphenadrine has the advantage of a euphoriant effect".

In the search for either an adjunct to enhance the somewhat limited benefits of, or as a more efficacious alternative to, medical treatment, many viewed surgery with what now in hindsight appears to have been unjustified hope. The fortuitous discovery by Cooper (1954) is well known: he ligated the anterior choroidal artery and hence damaged the medial globus pallidus, the ansa lenticularis, red nucleus and substantia nigra, and this produced dramatic improvement of tremor and rigidity.

Two years later, Cooper published (1956a; 1956b) detailed reports of clinical success through the use of surgical procedures aimed at destruction of the intact

grey matter of the globus pallidus and found that of the two procedures he had used, chemopallidectomy was more successful than anterior choroidal occlusion. Cooper's work received world-wide attention, and soon different neurosurgeons had perfected a variety of techniques (from the use of heat to high-frequency sound waves) for inducing subcortical lesions, with varying degrees of success. In 1969, at the *Third Symposium on Parkinson's Disease*, Gillingham, in his "Introduction to Scientific Sessions", claimed:

> By 1963 increased precision of stereotactic surgery had made bilateral lesions safer. This was an important step forward for bilateral parkinsonism has always been the hard core of the problem. Another five years of follow-up since the last Symposium have allowed surgeons to look more closely at the long-term effect of well-placed bilateral surgical lesions on the progress of parkinsonism. We are of course vulnerable in respect of measurement of the speed of deterioration before and after operation. This is a difficult problem *but there is no longer any serious doubt*, if we study patterns of daily activity before operation and during follow-up of 10 years or more, *that in an increasing number of patients the progress of the disease appears to have been greatly slowed down or even halted.*[1]

There are, however, those who do not subscribe to Gillingham's belief. The literature clearly does not bear it out (see Chapter 4 for a review of literature on this point, with particular reference to side-effects on speech); neither do the large number of post-operative patients who still return to Parkinsonian clinics and who are now on medical treatment (22 such patients are included in the present study). Indeed, the

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[1]writer's own italics

pessimism with which Schlesinger viewed the topic of stereotactic surgery as early as 1954, appears to reflect a more accurate evaluation of the efficacy of the technique:

> Surgery directed at the disturbed physiologic mechanisms of Parkinson's syndrome has produced much more in the way of laboratory insights than in clinical relief. No single operative approach to date has become a standard therapeutic tool. However, certain facts have been derived from the sum of various procedures. Chief among these is that rigidity responds poorly, even in proportion to the generally imperfect effect upon tremor.... The second conclusion to be drawn from surgical experience is that the efficiency of effect upon tremor, with notable exception, seems to be directly related to the degree of paresis incident to the procedure.

# CHAPTER 2

## FUNCTIONAL ANATOMY OF THE BASAL GANGLIA

Embedded in the white substance of each cerebral hemisphere are several bodies of grey matter. These were identified and described long ago. In 1543, Vesalius produced excellent woodcuts of various sections through the hemispheres to illustrate the shape and spatial relationship of these masses. They develop from the ectoderm layer of the primitive neural tube which bends over itself. Histologically, they are composed of motor-type (multipolar) cells. The functions subserved by these masses are not yet fully understood. Since they lie deep within the hemispheres, these structures are difficult to investigate by experimental methods. Until recently it had been almost impossible to place a lesion in one grey mass without inflicting damage on others, on adjacent fibre tracts, and, often, on superficial cortical structures as well (Brodal, 1969). The introduction of stereotactically produced lesions, more precise in localisation and more restricted in size than those of previous methods, and the use of silver impregnation for the tracing of connecting fibres, have made these grey bodies and their interconnections amenable to study.

Pathological changes in these bodies of grey matter have been observed in Parkinsonism. This chapter is intended to serve as a background to Chapter 3 which consists of a discussion of some current concepts of pathology in Parkinsonism. This chapter describes the parts concerned, their interconnections, and their biochemistry.

## TERMINOLOGY

A confusing system of terms has developed for these areas of the brain. As Brodal (1969) explained:

> In the course of time the term *"basal ganglia"* has carried different connotations. The old anatomists used it as a common denominator for all the large nuclei in the interior of the brain, including the thalamus. When the development of the brain became better known, the thalamus was excluded, while for instance, the amygadloid nucleus was included. There is still no generally accepted definition of what one should include in the concept *"basal ganglia"* although all authors consider the caudate nucleus and the lentiform nucleus with its two divisions, the putamen, and the globus pallidus, as representing the main mass. The claustrum is usually included, while the amygdaloid nucleus, on account of its largely different connections,and functions, is often excluded. It is common to consider the subthalamic nucleus and the substantia nigra in conjunction with the basal ganglia... The term *striate body* or *corpus striatum* is often used as almost synonymous with the basal ganglia and covers the claustrum, caudate, putamen, and globus pallidus. The name refers to the appearance in myelin-sheath-stained sections, where a number of myelinated fibre bundles traverse the cellular masses and give them a striated appearance.

To avoid confusion, in this and subsequent chapters, the terms 'basal ganglia' and 'basal nuclei' will be used interchangeably to comprise the striatum (caudate nucleus

+ putamen), pallidum, subthalamic nucleus, red nucleus, and substantia nigra. The term 'subcortical structures', is used as a usefully loose term which permits inclusion of the thalamus within its scope of reference.

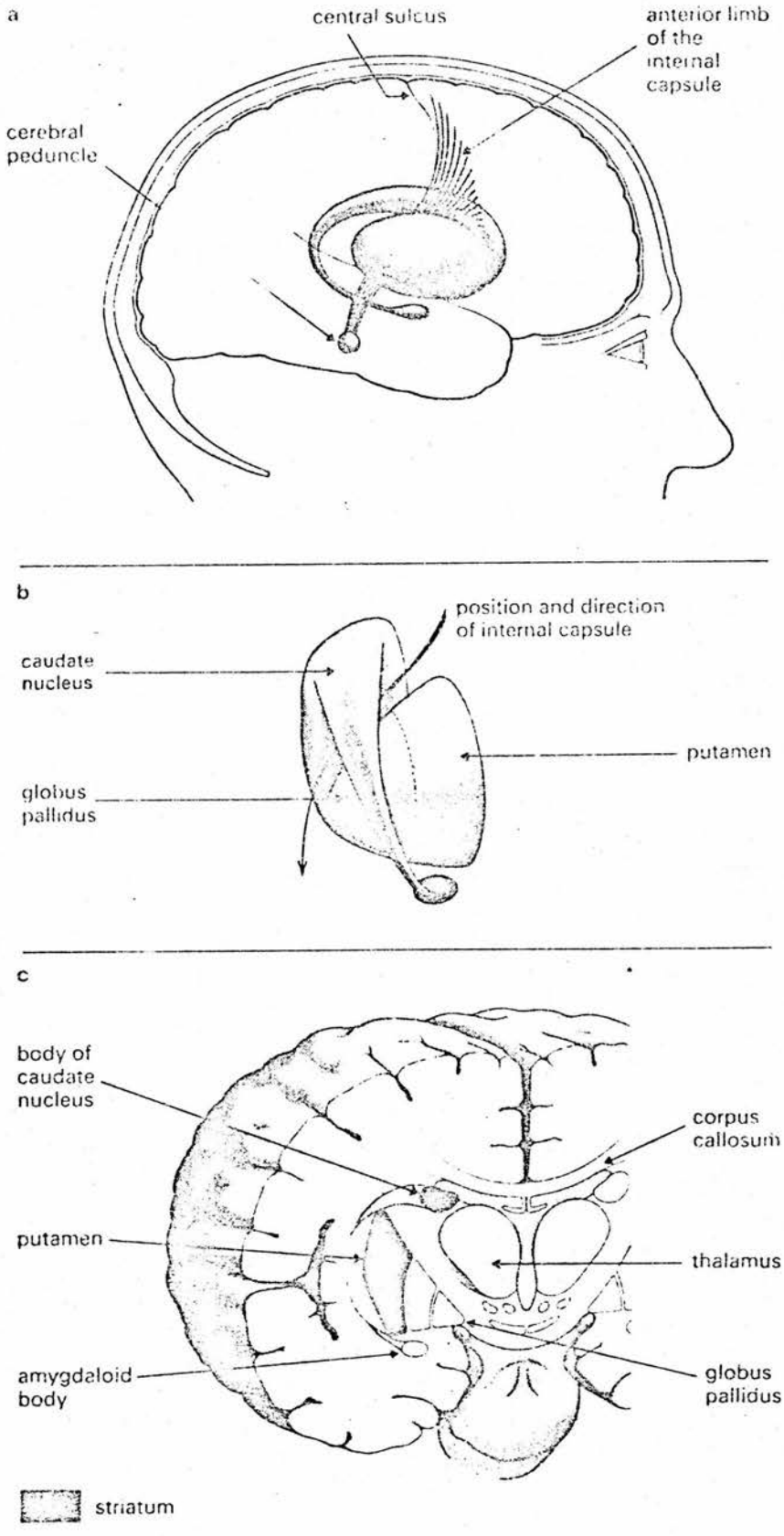
## THE SUBCORTICAL STRUCTURES

### THE CORPUS STRIATUM

The corpus striatum consists of three nuclei - the caudate, the putamen and the globus pallidus. The last two, the putamen and globus pallidus, are frequently referred to as the 'lentiform nucleus' though they are phylogenetically and histologically dissimilar. These structures are illustrated in FIGURE 1.

The *caudate nucleus* is an elongated c-shaped mass, so positioned that the lateral ventricle may be seen to curl around it. Its cephalic end (the *head*) is distended and bulges into the anterior horn of the lateral ventricle. Its *body* passes backwards, lateral to the thalamus and separated from it by the internal capsule, and tapers gradually around to form its *tail*. The tail of the caudate curves around into the roof of the inferior horn of the lateral ventricle, and extends rostrally as far as the amygdaloid nucleus. Within the curve described by the caudate lies the 'lentiform', comprising two other nuclei of the corpus striatum - the putamen and the globus pallidus (or pallidum).

DIAGRAMS TO ILLUSTRATE THE NEURO-ANATOMY OF THE BASAL GANGLIA




a. The corpus striatum viewed from its lateral aspect to show the relationship with the internal capsule and its position in the brain.
b. Posterior view of the basal ganglia.
c. A coronal section through the cerebral hemisphere to illustrate the relationships of the basal ganglia.

FIGURE 1

The *putamen*, the larger and more laterally situated of the two nuclei, is separated from the pallidum by the external medullary lamina, from the claustrum by the external capsule, and only partially from the caudate nucleus by the internal capsule. Anterior to the anterior limb of the internal capsule the putamen and caudate are joined together by bands of grey matter. As Ranson and Clark pointed out (1959), it is now customary to group the caudate nucleus together with the putamen as the 'striatum' (as opposed to the 'corpus striatum'). Histologically the two nuclei are similar, and, furthermore, they have the same phylogenetic development (together they constitute the 'neostriatum').

The *pallidum*, on the other hand, is a smaller, more medially situated nucleus, which differs from the striatum both histologically and phylogenetically. It is the oldest of the grey bodies (hence 'palaeostriatum'), and consists of multipolar cells and many myelinated fibres. It is the preponderance of these myelinated fibres that gives the pallidum its pale appearance. The pallidum is subdivided by the internal medullary lamina into an anterior-lateral and a posterior-medial portion. The pallidum is separated from the caudate nucleus, lying superior to it, and from the thalamus, medial to it, by the internal capsule. Caudally, however, the pallidum is continuous with the rostral area of the substantia nigra.

## THE SUBTHALAMIC NUCLEUS

The subthalamic nucleus, often referred to as the

'body of Luys' after the man who first identified it, is situated in the basal part of the diencephalon. It is roughly oval in shape, and both caudally and ventrally it is continuous with the substantia nigra. It is relatively large in man, is composed of medium sized multipolar cells, and this is histologically similar to both the pallidum and substantia nigra.

## THE SUBSTANTIA NIGRA

The substantia nigra is particularly well developed in man. It can be seen with the naked eye as a thick, darkly coloured strip. Situated in the cerebal peduncle of each side of the mid-line, it extends from the sub-thalamic region down in the mid-brain. The substantia nigra is composed of two sections, the dorsal 'zona compacta' and the ventral 'zona reticularis'. Its dark appearance is due to the abundance of melanin dispersed in the cytoplasm of its cells, particularly in the zona compacta. Histologically the substantia nigra resembles the two nuclei with which it is in close anatomical connection, the pallidum and the subthalamic nucleus.

## THE RED NUCLEUS

The red nucleus is situated within the upper part of the substance of the mid-brain, at the level of the superior colliculi. It comprises two distinct grey masses - the magnocellular and the parvicellular divisions.

## THE THALAMUS

The thalamus is a large nuclear mass comprising the dorsal portion of the diencephalon. It lies immediately lateral to the third ventricle, and is bound laterally by the internal capsule. The epithalamus lies above it, the subthalamus below and behind, and the hypothalamus below and in front of it. Internally, the thalamus is divided into anterior, medial, lateral, ventral and central nuclear groups. Each of these is further subdivided according to their different connections.

# CONNECTIONS OF THE SUBCORTEX

## CORTICAL-SUBCORTICAL CONNECTIONS

### Cortico-striatal Connections

It appears that *all* parts of the cerebral cortex project fibres to the striatum (Glees, 1944; Mettler, 1945; Carman, Cowan and Powell, 1963; Webster, 1961, 1965). Furthermore, these projections are topologically organized. Carman, Cowan, Powell and Webster (1965) demonstrated that anterior cortical lesions result in degeneration in anterior parts of the striatum, and posterior cortical lesions cause degeneration in its posterior parts. They also showed that most of this cortico-striatal projection is ipsilateral. The only area to have bilateral connections is the primary

sensorimotor cortex. The contralateral connection is established by fibres crossing in the corpus callosum. Innervation reaches the caudal part of the head of the caudate through the fasciculus subcallosus, and the putamen through the external capsule.

Cortico-subthalamic Connections

Mettler (1945) established that (in the monkey) efferent fibres connect Brodmann's area 6 with the subthalamic nuclei. Subsequently, (again, in the monkey) a connection was found between the prefrontal lobe and the subthalamic nuclei (De Vito and Smith, 1964). Meyer (1949) has presented evidence to suggest that these fibres also exist in man. The fibres appear to end in the cellular region rostral and dorsal to the subthalamic nucleus, in the zona incerta.

Cortico-nigral Connections

In 1966 Rinvik found a tenuous cortico-nigral connection in the cat. He felt that this apparent contradiction of early findings of a more substantial connection might be due to differences of experimental technique. He suggested that when using the Marchi method (as opposed to the Nauta and Gees methods) it is easy to misidentify a set of fibres as ending in the substantia nigra when in fact they merely pass through, to end in the red nucleus and reticular formation.

The projection from the cortex is, according to Rinvik, predominantly ipsilateral, descending through the internal capsule and cerebral peduncle. It arises

from the primary and secondary sensorimotor cortices, supplementary motor area, and the gyrus proreus (in the cat this is in front of the primary sensorimotor area).

Rinvik's description, however, is substantially different from that given by Jung and Hassler (1960). They described a "major pathway of efferent fibres" from the frontal cortex (areas 9 - 12) to the anterior part of the substantia nigra, and a contralateral projection from the cortical area 6 and from precentral, parietal and temporal areas to the large cells of the posterior part of the substantia nigra.

## INTER-SUBCORTICAL CONNECTIONS

### The Striatum

The striatum receives fibres from the centrum medianum of the thalamus. From the dorsal part of the nucleus, larger cells project to the caudate, and, from the ventral part, smaller cells project to the putamen (Nauta and Whitlock, 1954; Powell and Cowan, 1956). It is suggested that the striatum receives another set of fibres - the nigro-putamen pathway (Mettler, 1964; Carpenter and McMasters, 1964).

The striatum itself projects fibres to at least three, and probably four, different areas within the subcortex. It sends most of its efferent fibres (via the *strio-pallidal connection*) to its neighbouring pallidum. These caudate →pallidum and putamen→pallidum connections have been shown to exist in the cat (Johnson and Clemente,

1959; Voneida, 1960), and in the monkey (Szabo, 1962; Nauta and Mehler, 1966). The most interesting finding, however, was made by Cowan and Powell (1966). They showed that the striatopallidal projection is topologically organized: each part of the striatum sends fibres to a circumscribed part of the pallidum. According to Cowan and Powell, however, it is not possible to differentiate between the two segments of the pallidum on the basis of these striatopallidal projections. This is in direct contradiction to the findings of Jung and Hassler. According to them, the pallidum receives afferent fibres (striopallidal, and others) in only the external segment; the internal segment receives afferent fibres only from the external segment.

The strionigral connections are the second set of efferents emerging from the striatum. The caudate nucleus sends efferents - along the ventral surface of the internal capsule - to the anterior part of the substantia nigra. In addition, a small number of fibres lead to the posterior part. The putamen sends its efferents through the pallidum and peduncle to the large cell groups of the posterior substantia nigra (Jung and Hassler, 1960; Szabo, 1962).

The third set of efferents from the striatum lead to 'restricted parts' of the inferior olive (Walberg, 1956).

Finally, there is a strong possibility that the striatum sends fibres to the subthalamic nucleus (Hassler, 1949).

The Pallidum

The major afferent projection to the pallidum, as already described, comes from the striatum, (which in turn receives afferents from all cortical areas). This is a topologically organized connection. Thus, different parts of the pallidum are influenced, via the striatum, by specific regions of the cortex.

The efferent fibres leaving the pallidum are numerous. Brodal (1969) has described them:

> The *efferent fibres from the pallidum* form rather massive bundles which were observed by the classical neuro-anatomists and labelled by them. Unfortunately, there is much confusion in the literature concerning nomenclature... Most authors describe a fairly compact bundle, the *ansa lenticularis*, emerging from the ventral aspect of the inner segment of the pallidum and turning in a mediocaudal direction... A branch of the bundle, taking a more dorsal course, is often referred to as the *fasciculus lenticularis*, $H_2$-bundle or dorsal division of the ansa... This appears to arise more dorsally than the ansa proper. A middle division of the ansa is sometimes referred to as the *subthalamic fasciculus*, passing to the nucleus of the same name.

The pallidum thus sends efferents to the thalamus, to the substantia nigra, the subthalamic nucleus, the red nucleus, the mesencephalic reticular formation, the inferior olive, and the hypothalamus.

Nauta and Mehler (1966) confirmed the original statement by Ranson, Ranson and Ranson (1941) that fibres of the ansa originate only from the internal segment of the pallidum. However, they found that fibres to the subthalamic nucleus are an execption. These arise from the external segment, and furthermore, they are organized topologically. It is not yet known whether

other efferent projections from the pallidum are similarly organized.

The Subthalamic Nucleus

The subthalamic nucleus receives afferents (topologically organized) from the cortex, from the pallidum, and probably from the striatum. Some efferent fibres pass through the fasciculus of Forel to the pallidum and the putamen, and others lead to the thalamus. In addition, the subthalamus communicates through the subthalamotegmental tract with the tegentum of the mid-brain, and through the supramamillary decussation of Forel, with the contralateral subthalamic nucleus. Furthermore, it has been hypothesized that the subthalamus has connections with the red nucleus and with the substantia nigra (DeJong, 1967).

The Substantia Nigra

The corticonigral and strionigral afferent connections have already been mentioned. In addition, the substantia nigra receives afferents from the tegmental nuclei, and possibly also from the red and subthalamic nuclei (DeJong, 1967).

In its turn, the substantia nigra establishes numerous sets of connections. It sends efferent fibres to the superior colliculus, to reticular (mesencephalic) formation, and to the red nucleus (Llamas and Reinoso-Suárez, 1969); it sends efferents to the thalamus, i.e. to the ventrolateral, ventromedial and ventro-anterior thalamic nuclei (Cole et al., 1964 ; Afifi and Kaelber,

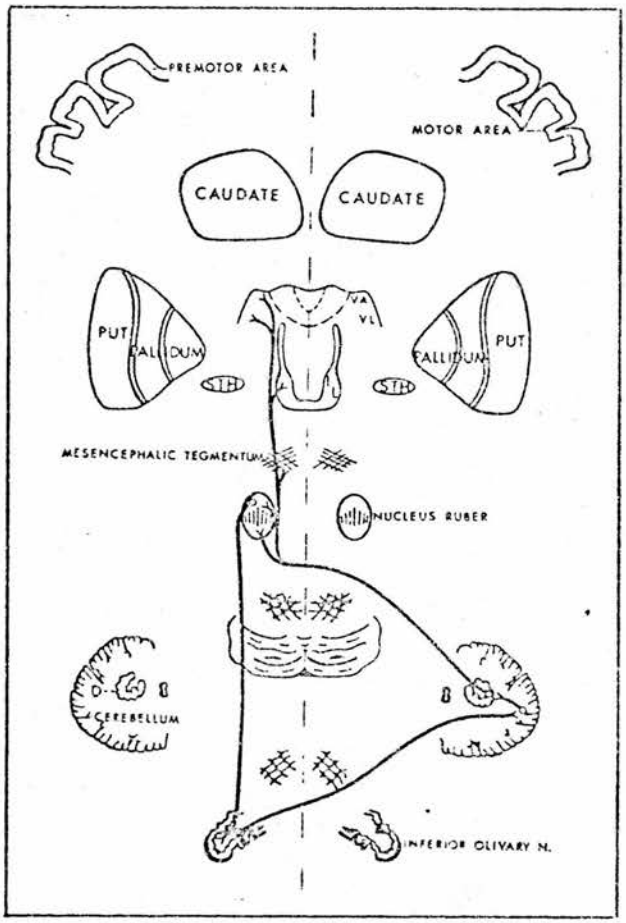
1965; Carpenter and Strominger, 1967; Llamas and Reinoso-Suarez, 1969); it sends efferents to the internal and external segments of the pallidum and to the putamen (Ferraro, 1925, 1928; Llamas and Reinoso-Suarez, 1969; but not shown in studies using silver impregnation methods by Carpenter and McMasters, 1964; Cole et al., 1964; Afifi and Kaelber, 1965; Carpenter and Strominger, 1967); to the head of the caudate nucleus (Llamas and Reinoso-Suarez, 1969 which is in agreement with the physiological results of Frigyesi and Purpura, 1967); and finally, to areas 4 and 6 of the cerebral cortex (Llamas and Reinoso-Suarez, 1969; confirming the description by von Monakow, 1822, 1895; Molina, 1965; Llamas and Reinoso-Suarez, 1969; but denied by Ferraro, 1925).

The Red Nucleus

The red nucleus which receives afferents from the cortex (Poirier, 1971), from the substantia nigra (see above) and from the pallidum, gives off a complex system of efferents (see FIGURE 2). The parvicellular area gives rise to fibres which end in the ipsilateral inferior olive (Poirier and Bouvier, 1966). From here, a neural loop is elaborated to the contralateral cerebellar cortex, then to the cerebellar nuclei, and, from there, back again to (the now contralateral) red nucleus (Poirier, 1971). (There are other parallel loops at this level establishing contralateral connections - see Poirier, 1971). Importantly, cortical connections are

established with these nuclei - from the precentral gyrus to the red nucleus, to the tegmentum and to the olive.

THE RUBRO-OLIVO-CEREBELLO-RUBRAL LOOP[1]




[1]*from Poirier, 1971.*

FIGURE 2

The Thalamus

The thalamus receives all the sensory pathways of the central nervous system: somatosensory fibres in the ventroposterior nucleus; auditory fibres (the lateral lemniscus) in the medial geniculate body; optic fibres in the lateral geniculate body; and finally, fibres from the cerebellum, red nucleus and pallidum in the ventrolateral nucleus. Together these four nuclei form the

*ventral complex of nuclei* in the thalamus. They have two important characteristics. Unlike the other five chief thalamic nuclei groups, the ventral group receive their *total* afferent input from nuclei lying outside the thalamus, and they project all their efferents, somatotopically organized, to the primary motor and sensory areas of the cortex.

The intralaminar group of the thalamic nuclei (which includes the centrum medianum) has rather complicated connections. Afferents are from two sources - from within the thalamus, from the other nuclei; and from outside the thalamus, from the ascending reticular system. Efferents are specific and diffuse. There are somatotopically organized connections with the caudate and putamen, and (probably via the thalamic reticular nucleus) diffuse connections with the whole cortex.

The four other groups of thalamic nuclei receive fibres from within the thalamus, and project in a topologically organized manner to the cortex. The large dorsomedial groups project to the frontal lobe; the anterior group to the cingulate gyrus; the lateral group together with the pulvinar project to the association areas of the cortex in the parietal and occipital lobes.

Thus, there are both specific and non-specific thalamocortical connections. Bowsher (1962) emphasized the importance of these connections to concepts of the cerebral cortex:

Thus the whole telencephalon, except some of the

neocortex of the temporal lobe, can be regarded as an umbrella cover, whose hub is the thalamus and the spokes of which are the specific point-to-point thalamo-telencephalic projections... It can be seen from this that the true definition of a functional cortical area depends not upon the fortuitous folding of its surface into sulci and gyri, not upon its cytoarchitecture (though this is related), but upon its specific projection from a particular thalamic nucleus. For example, the primary and somatosensory cortex (roughly defined as the postcentral gyrus) is, in precise terms, only and entirely that area of cortex which receives its specific projections from the ventroposterior nucleus of the thalamus. Primary motor and sensory areas, as well as the hypothalamic-rhinencephalic areas of the neocortex, are easily understood as those cortical areas which receive their specific projections from thalamic nuclei whose afferents are extra-thalamic. The parieto-occipital association areas, on the other hand, receive their specific projections from thalamic nuclei whose afferents are intrathalamic (lateral-pulvinar group). Specific thalamo-cortical fibres may be seen to terminate in the fourth layer of the cortex, where they are known as the outer stripe of Baillarger.

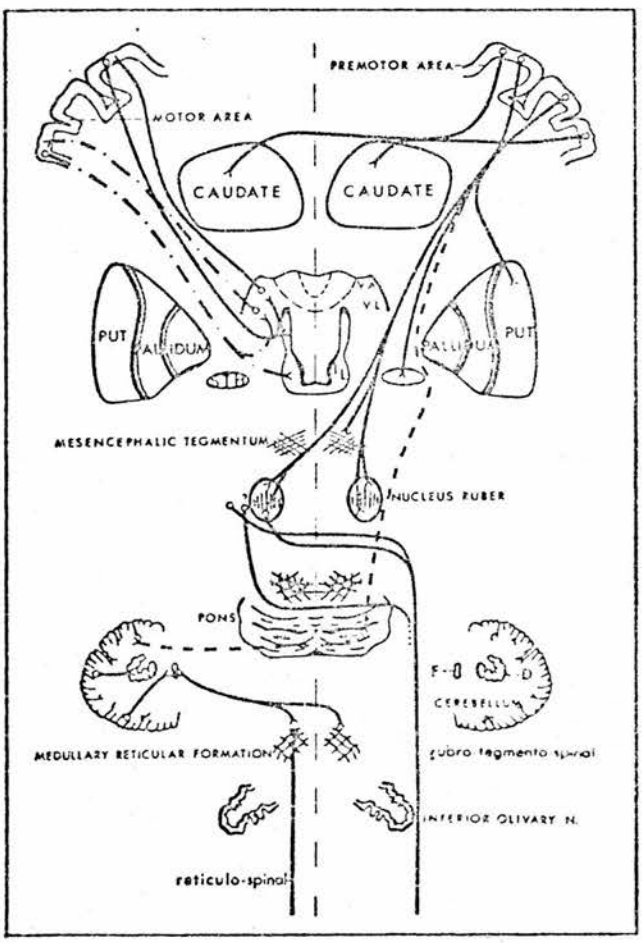
## SUBCORTICO-MOTONEURONE CONNECTIONS

There are two descending connections arising from the basal ganglia which together represent the final pathway for motor impulses originating in the cortex, and relayed through subcortical structures, to the motor neurones of the spinal cord.

Major descending fibres arise in the magnocellular division of the red nucles (see FIGURE 3). They cross to the contralateral side (Poirier and Bouvier, 1966), and most of the fibres descend in the spinal cord. Two other groups of descending fibres, apparently of tegmental origin, join the rubro-spinal fibres. According to Poirier and Bouvier (1966) one group crosses the mid-line (more rostrally in the ventral tegmental decussation than

do the rubro-spinal fibres) and send at least some fibres to the spinal cord; and, according to Poirier et al. (1969a), another group of tegmental fibres join the rubro-spinal tract at the level of the superior olive. It has not yet been established whence these fibres lead (Poirier et al., 1969b).

THE RUBRO-SPINAL TRACT[1]




[1]*from Poirier, 1971.*

FIGURE 3

As has previously been described, the red nucleus and its surrounding tegmentum receive fibres from (contralateral) cerebellar nuclei, the (ipsilateral) precentral gyrus, the (ipsilateral) pallidum, and the

(ipsilateral) substantia nigra. This rich afferent input has lead Poirier (1971) to suggest that "the rubrospinal fibres and the accompanying descending tegmental fascicles probably represent the most important extrapeduncular pathways reaching the spinal cord from the upper brain stem. They constitute the crossed rubrospinal tract." Massion (1967) has shown the tract to be somatotopically organized and to be involved in the excitation of $\alpha$-motor neurones and static to $\gamma$-motor neurones of flexor muscles.

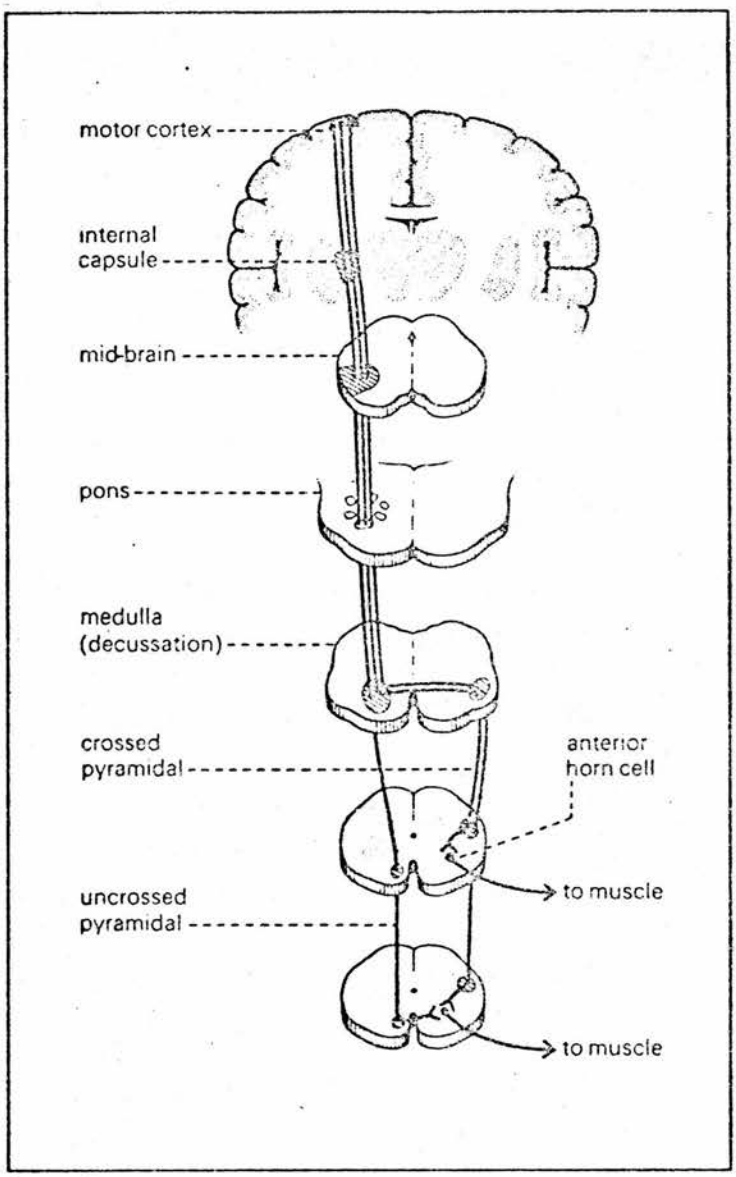
The second major descending tract (see FIGURE 13 on page 74) arises from the striatum and the pallidum. It leads to the (ipsilateral) gigantocellular nucleus of the medulla. From this medullary reticular nucleus, fibres descend as the medial reticulospinal tract and end at the alpha motor neurones of the spinal cord (Denny-Brown, 1969). The gigantocellular nucleus corresponds to the 'inhibitory area' described by Magoun and collaborators (Magoun and Rhines, 1946; Lindsay, Schreiner and Magoun, 1949). Fibres also arise from pontine reticular nuclei ("facilitation area" of Rhines and Magoun, 1946; or, more cumbersomely, "nucleus reticularis pontineoralis" and "nucleus reticularis pontis caudalis", Brodal, 1969), and descend to the spinal cord as part of the reticulospinal tract. According to Brodal (1969), the medullary contribution consists of both crossed and uncrossed fibres; the pontine contribution is uncrossed. There appears to be no somatotopical patterning within the reticulospinal projections.

A complex system has been described whereby impulses from the motor cortex (in particular) may impinge on the motor neurones of the spinal cord and cranial nerve nuclei. The system is conventionally referred to by the unsatisfactory term (see Meyers,1953) 'extra-pyramidal' to distinguish it from the direct corticospinal ('pyramidal') tract which passes from the motor cortex, down through the internal capsule (in a somatotopically organized manner), to the level of the medullary pyramids where (the majority of) its fibres decussate across the mid-line, and then descend in the lateral column of the spinal cord to synapse onto the motor neurones there. (see FIGURE 4)

The 'extra-pyramidal' system, in contrast, is a highly complicated, multisynaptic, interconnected motor system. It receives cortical afferents (via the cortico-striatal, cortico-subthalamic, cortico-rubral, cortico-nigral and cortico-claustral connections). It returns efferents to the cortex (via the diffuse centrum medianum - cortical connection, the specific thalamo-cortical connection established by the ventral thalamic nuclear group and the nigro-cortical connection to cortical areas 4 and 6). It communicates with the motor neurones of the spinal cord and cranial nerve nuclei through two major tracts - the rubro-spinal and the reticulospinal. Between the input and the output

is a system of interconnection loops; a network of connections providing for sophisticated bilateral sensorimotor feedback and modification of input. (see FIGURE 5)

THE 'PYRAMIDAL' TRACT[1]




[1]*from Tilleard-Cole and Marks (n.d.).*

FIGURE 4

THE 'EXTRA-PYRAMIDAL' TRACT

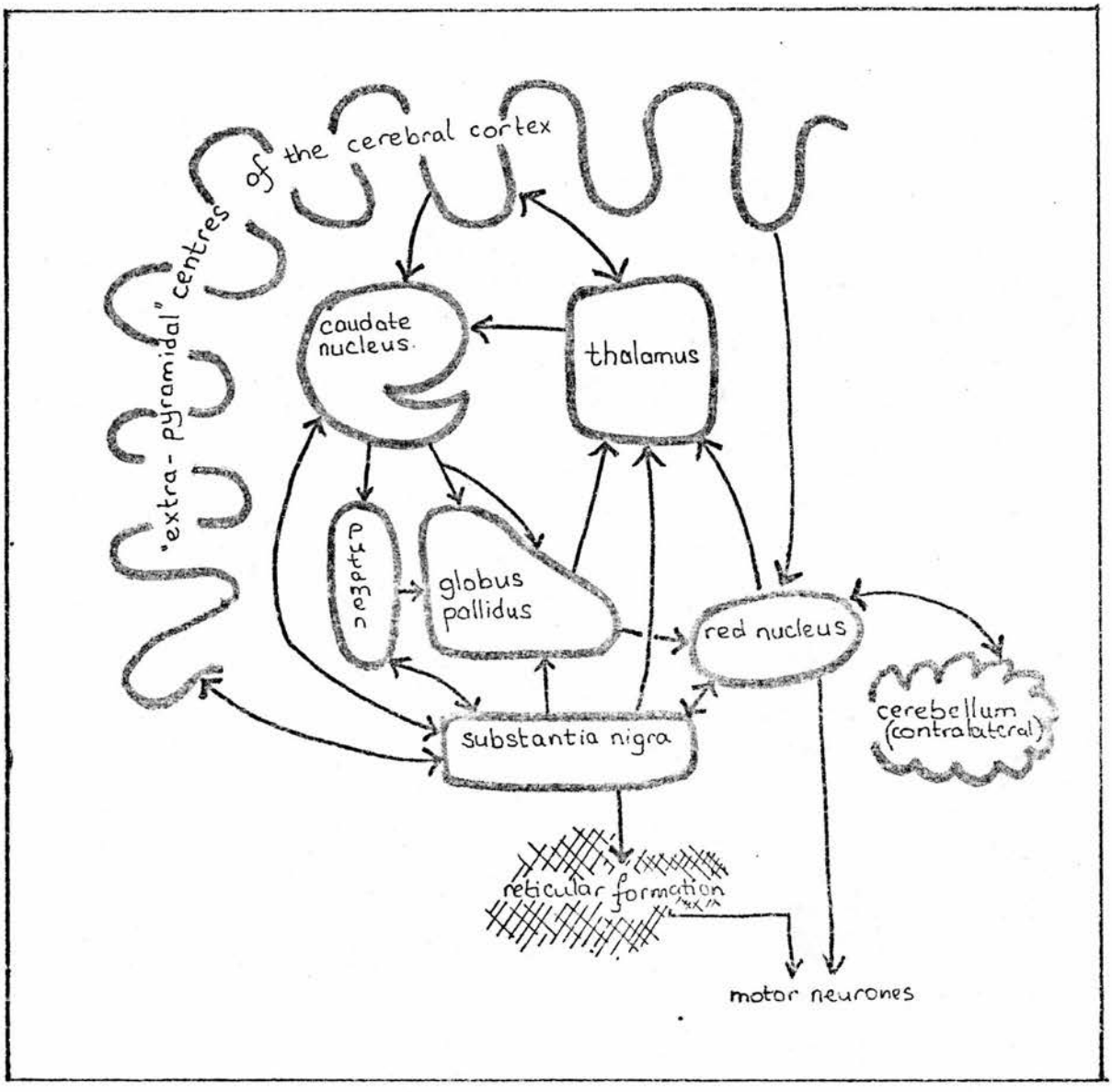



FIGURE 5

THE SYNAPSE

Central to our understanding of the function of the subcortical nuclei, is an understanding of the synapse and the chemical basis upon which the synapse depends.

'Synapse', a term derived from the Greek for 'to clasp', was introduced by Sherrington (1897). It refers to the point where the axon terminal of one nerve cell comes into functional contact with another nerve cell. Over the past 70-odd years, we have learnt much of the synapse; in the beginning, however, progress was slow, paced by the limitation of technique and equipment.

> By the turn of the century the light microscope was already exploited to its limits of resolution and the major stains, usually involving silver salts, had been developed to reveal the nerve fibres and their synaptic contacts. However, the limited resolution revealed little specialized structure at the synapse other than a bulbous expansion or, sometimes, a curious ring shaped or tennis racket like structure at the axon terminal.
>
> While such synaptic structures could be demonstrated in lower centres of the nervous system, particularly in the spinal cord which is directly concerned with muscle control, reflexes and so on, the silver stains essential for light microscopy failed entirely to reveal any such synaptic bulbs or rings in the higher brain centres such as the cerebral cortex. Many workers therefore regarded the cortex as a highly specialized part of the nervous system where the nerve cells reacted with one another in some complex manner that did not involve the sort of synaptic contacts found in the lower centres. Another enigma was the presence of numerous small spines projecting from the surface of dendrites in the cerebral cortex.
>
> The interpretation of these structures and whether there was protoplasmic continuity across the synapse or whether it was a region of discontinuity, having a minute gap beyond the resolution of the light microscope, caused much concern with the classical investigators, Hans Held, Santiago Ramon-y-Cajal and Camillo Golgi amongst others. Synaptic detail was clearly beyond their grasp... (Grey, 1967).

Although it proved difficult to learn of the structure of the synapse, the physiology of the synapse was better understood. In 1939, J.Z. Young inserted electrodes into the pre- and post-synaptic component of the giant synapses in the squid, and was thus able to register and stimulate impulses. Much of our knowledge

of synaptic functioning dates from this work. It is clear that the transmission of nerve impulses across the synapse is a chemical process. The nerve impulses arriving at the axon terminal cause a chemical to be released. This transmitter substance rapidly diffuses across the intersynaptic cleft, excites the post-synaptic terminal, and is then destroyed.

Early work concentrated on acetylcholine which is manufactured by the acetylation of the fat choline with acetyl-CoA, by the enzyme choline acetylase, and destroyed post-synaptically by the enzyme cholinesterase. (see FIGURE 6). Acetylcholine is a transmitter substance between nerves and muscles; it is important, and vulnerable. "Anything which interferes with the diffusion of the transmitter across... [the synaptic cleft] will prevent the message being passed on, and many drugs which interfere with acetylcholine or with its subsequent destruction by cholinesterase thus block synaptic transmission and result in a sort of chemical paralysis." (Rose, 1970).

Sir John Eccles (1964), and his colleagues, developed a technique for inserting extremely small electrodes into single neurones. On the basis of investigation using this technique, they were able to draw at least two important conclusions: firstly, that the brain and spinal cord *do* have a chemical basis of transmission; and, secondly, that there are two types of synaptic activity - excitatory and inhibitory.

TRANSMISSION OF AN IMPULSE THROUGH A CHOLINERGIC SYNAPSE

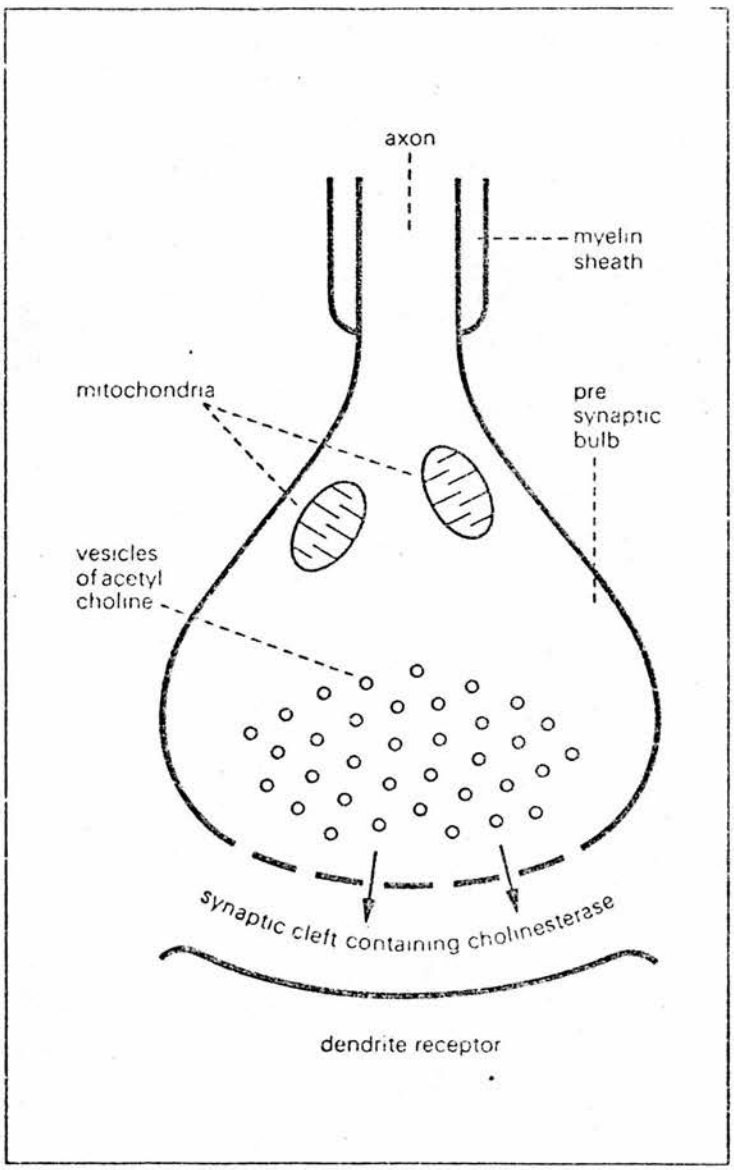



FIGURE 6

In the early 1950's, knowledge of the synapse was more advanced in physio-chemical terms than in terms of structure. However, the introduction of the electron microscope dramatically changed the situation. "Then for the first time", according to Grey (1967), "we were able to obtain high resolution pictures of thin sections

of the brain, showing its minute structure with great clarity and revealing an enormous complexity that in many respects is still far from understood."

The axonal bulb of the synapse (1-2μ across) is surrounded by a thin surface membrane. Oval bodies, the mitochondria, and swarms of small spherical capsules, the vesicles, lie inside the bulb. (see FIGURE 7). The

REPRESENTATION OF AN ADRENERGIC NERVE ENDING

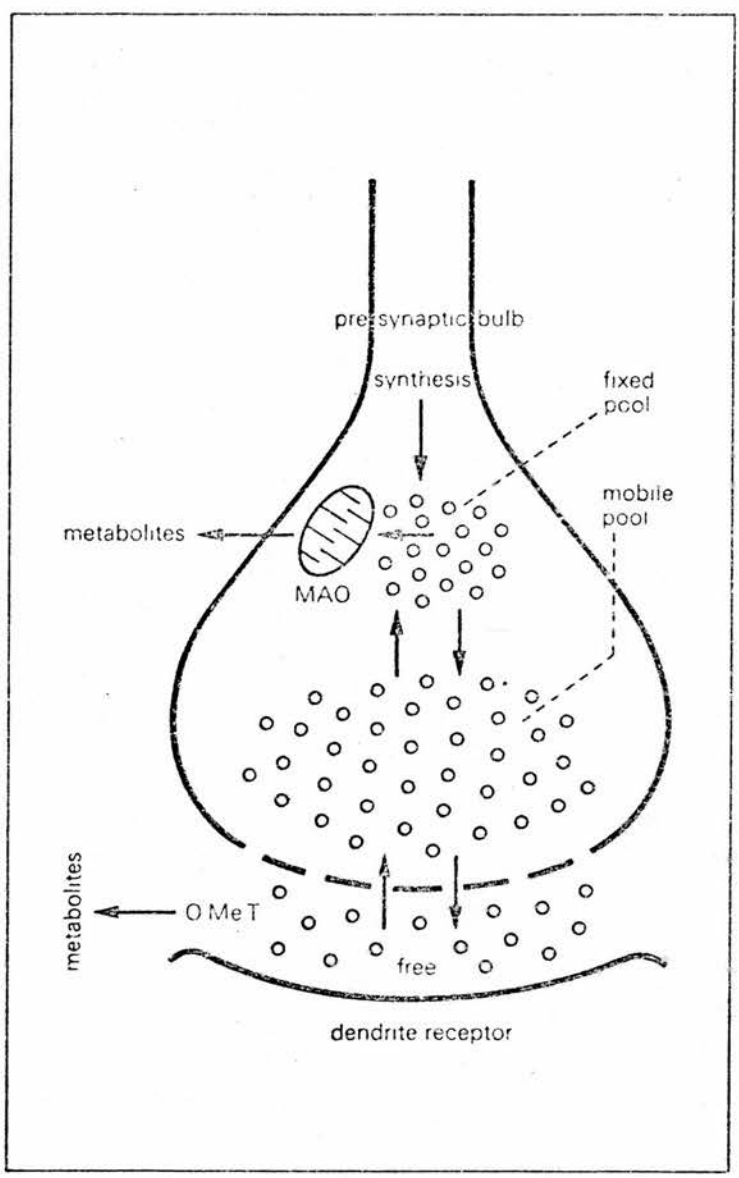



FIGURE 7

pre- and post-synaptic bulb are separated by a 200Å cleft, which, as Eccles (1964) pointed out, is an extracellular zone narrow enough to permit rapid diffusion of a transmitter substance across the cleft for 'split second' responses. Seen under a microscope, the vesicles appear to be moving towards the synaptic cleft, and aggregate near the pre-synaptic membrane. They are believed to contain the transmitter substance. The mitochondria, which occur not only in the pre-synaptic bulb but also in the post-synaptic dendrite or cell body, provide 'fuel' by liberating energy-rich adenosine triphosphate (ATP).

The physiological action of the catecholamines within the central nervous system is not well understood. The current theory, which holds that monoamines are stored within the synapse in two forms, is concisely and simply explained in terms of the adrenergic system by Tilleard-Cole and Marks (n.d.):

> The monoamines are thought to exist in the tissues in a stored and in a free form. The free amines show biological activity and are capable of being metabolized by O-methyltransferase. The stored amines occur in two storage sites within the neurone in special storage granules, are biologically inactive and are protected from metabolism by the granule covering. Part of the storage amines, located close to the nerve endings, is released into the synaptic space on nerve stimulation. There it stimulates the adrenergic receptor and is then inactivated. Some 95 per cent of this inactivation occurs by restorage in the granules and only a small fraction is metabolized by O-methyltransferase...
>
> The second monoamine storage pool is situated in the vicinity of structures containing monoamine oxidase (i.e. mitochondria). A balance exists between the two intracellular storage areas, but any catechol amine released from the second storage area is metabolized by monoamine oxidase before it exerts a physiological effect.

In the central nervous system, however, practically

the entire monoamine content is localized in enlargements, the varicosities, of the monoamine nerve terminals (Fuxe et al., 1969). These varicosities are believed to represent the pre-synaptic structures where the amines are synthesized, stored, released and broken down (Fuxe, 1965a). Moreover, Hökfelt (1968) has provided direct morphological evidence that the varicosities make synaptic junctions with cell bodies and with dendrites. Anden et al. (1966) found that the monoamine cell bodies contain only low concentrations of amines (10-100 µg/g); the axons arising from these cell bodies also have very low concentrations until they are transformed into the terminal parts which have high amine concentrations (1,000-10,000 µg/g).

## TRANSMITTER SUBSTANCES RELEVANT TO SUBCORTICAL NUCLEI

Several transmitter substances play a significant role in the central nervous system. These are the amines - serotonin (5-hydroxytryptamine), noradrenaline, dopamine, and acetylcholine. Each of these amines functions in a separate system (Fuxe et al., 1969). Neurones and their synaptic contacts are, therefore, generally defined according to the chemical nature of their neurotransmitter; for example, 'dopaminergic neurones' are those which have dopamine as their transmitter.

Although the dopaminergic system has come to occupy an increasingly important place in relation to Parkinson's disease, all the amine systems are intimately interrelated. The early work which discovered noradrenaline and serotonin in the brain, and the effect of reserpine on these amines illustrates this well. In the mid-fifties, Marthe Vogt (1954) reported that noradrenaline (NA) was distributed within the mammalian brain and that certain drugs were capable of altering the levels of noradrenaline concentration. Simultaneously, serotonin (5-HT), another biogenic amine was detected (Amin et al., 1954; Twarog and Page, 1953), and the serotonin-blocking action of lysergic acid diethylamide (LSD) on peripheral tissues (Woolley and Shaw, 1954). This led to speculations on the role of this amine in mental functions, and another important discovery was made - the neuroleptic agent, reserpine, releases serotonin from its tissue stores. Moreover, reserpine was found to have more widespread effects; in addition reserpine depletes tissue stores of adrenaline (Holzbauer and Vogt, 1956). This depletion of amine stores leads ultimately to transmission failure of peripheral adrenergic nerves. Carlsson et al. (1958) demonstrated in experimental animals that this reserpine-induced syndrome is "dramatically" reversed by the administration of L-dopa.

Although levels of amine concentration are undoubtedly important, it may well be the ratio between different amine-levels or the turnover of dopamine that



is fundamentally important in maintaining normal functioning of the motor system.

## SEROTONIN

Tryptophan is hydroxylated and then decarboxylated to produce serotonin (5-hydroxytryptamine, or 5-HT). Serotonin is catabolised by an oxidative deamination, yielding as the main end-product 5-hydroxyindole 3-acetic acid (5HIAA); the enzyme involved in the reaction is monoamine oxidase. (see FIGURE 8)

BIOSYNTHESIS AND METABOLISM OF SEROTONIN (5-HT)

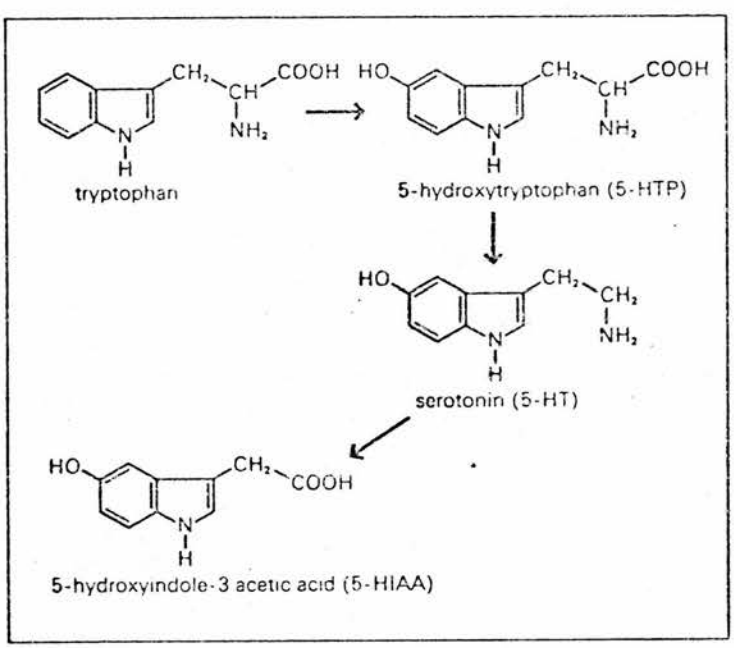



FIGURE 8

Serotonin is found in several subcortical nuclei. Fuxe (1965) identified serotonin-containing nerve terminals in both the pallidum and the substantia nigra; and Tilleard-Cole and Marks (n.d.) state that "high

concentrations [of serotonin] are found in the hypothalamus and caudate nucleus with lower concentrations in other grey matter. Negligible amounts of serotonin are found in areas which consist predominantly of myelinated fibres." However, according to Fuxe et al. (1969), it is the limbic mid-brain area that contains the largest amount of serotonin cell bodies in the brain.

The effect serotonin has upon these structures and upon behaviour has been investigated to a limited extent. Its action has been described as being predominantly depressant in the caudate (Herz and Zieglgänsberger, 1968) and in the ventrolateral nucleus of the thalamus (Phillis and Tebécis, 1967). The administration of serotonin plus a monoamine oxidase inhibitor, to animals, increases brain serotonin levels of concentration. "Such elevation of serotonin produces behavioural changes similar to those resulting from the administration of lysergic acid diethylamide (LSD)." (Tilleard-Cole and Marks, n.d.). Andén et al. (1969) have shown serotonin to be involved in thermoregulation; in the hypothalamus, for example, serotonin actively decreases in hypothermia and increases in hyperthermia.

## NORADRENALINE

The biosynthesis and metabolism of noradrenaline, according to Grey (1967), have been well worked out. Phenylalanine, an essential amino acid, is converted to

tyrosine; tyrosine is hydroxylated to yield dopa; L-dopa, in turn, is decarboxylated to dopamine; dopamine is hydroxylated to give noradrenaline. Methylation of noradrenaline produces adrenaline. This last stage is believed to take place outside the central nervous system (see FIGURE 9)

BIOSYNTHESIS AND METABOLISM OF NORADRENALINE AND ADRENALINE

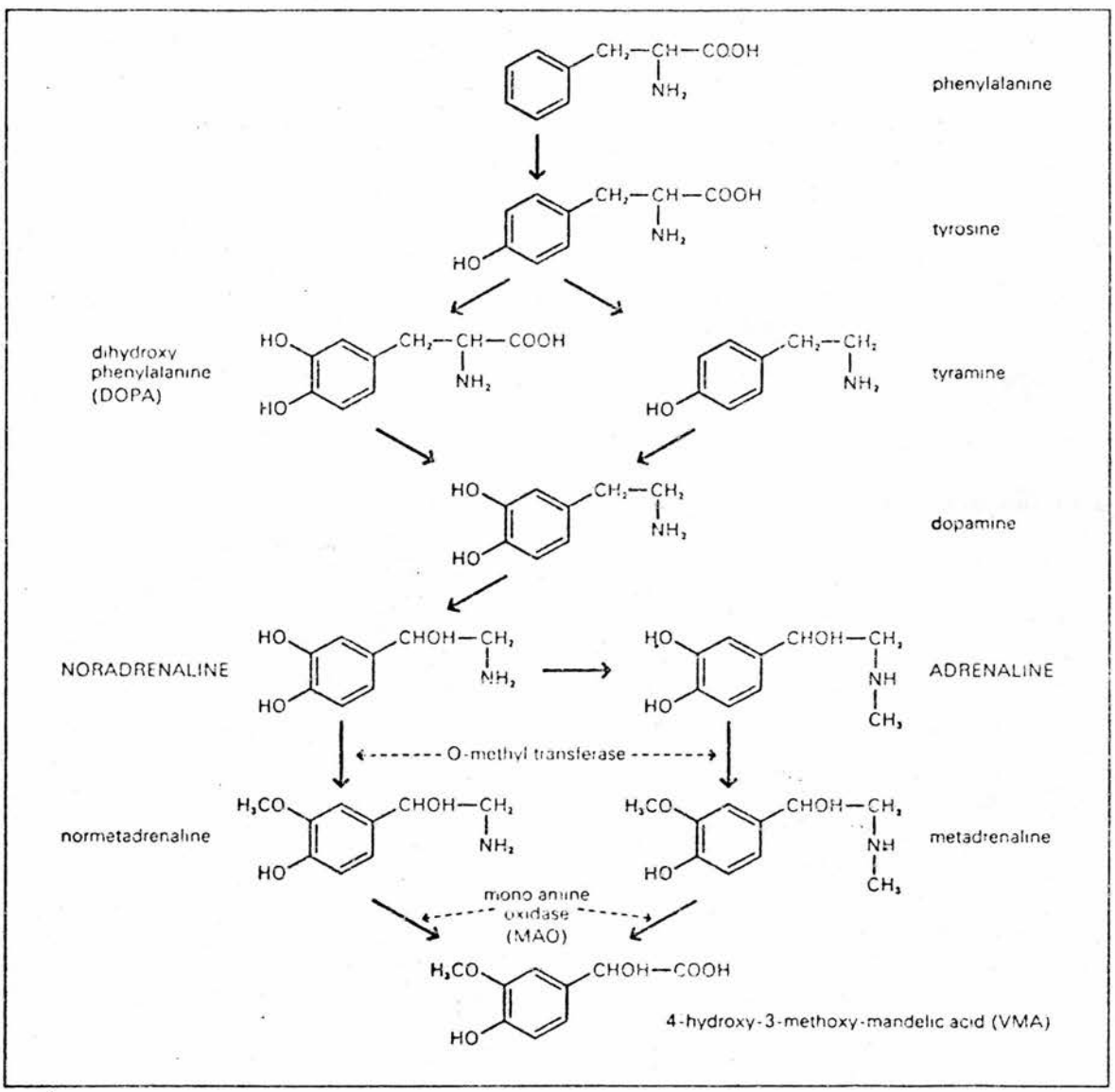



FIGURE 9

Carlsson, Falck and Hillarp (1962), using a histochemical fluorescence method, were the first to find indications of noradrenaline localized in the central nervous structures. The largest concentration of noradrenaline is to be found in nerve terminals of the hypothalamus. According to Fuxe et al. (1969) these adrenergic nerve terminals exhibit the thickest varicosities in the brain (1-1.5μ). Noradrenaline is also found with considerable variations of concentration throughout the terminals in the reticular formation; the highest concentration is in the area surrounding the superior cerebellar peduncles (Fuxe, 1965 ). It is also found in the mid-brain tegmentum, the bulb, the thalamus (particularly the medial thalamus, but also, in lesser quantities, in the ventrolateral) (Adam, 1969), and in the zona reticulata of the substantia nigra (Fuxe et al., 1969). Afferent, adrenergic terminals to the cortex have been described by Fuxe et al. (1968). These afferents do not exhibit any distinct cytoarchitectonic patterns. Instead they are diffusely distributed throughout cortical areas; the cingulate region, in particular, receives a "high density" of afferents.

## ACETYLCHOLINE

It has long been established that acetylcholine is a neurotransmitter substance at the neuromuscular junction, in all automatic ganglia (i.e. adrenergic and cholinergic) and in post-ganglionic cholinergic terminals.

This physiologically highly potent compound is also found in the mammalian brain where it is considered to fulfil the role of a central neurotransmitter (Hornykiewicz, 1971).

(See the preceding section - *The Synapse* - for a description of the metabolic pathway of acetylcholine).

Acetylcholine is an extremely labile compound; early studies of the distribution of acetylcholine relied on the occurrence of the synthesizing enzyme choline acetylase as an indicator of the presence of acetylcholine (Feldberg and Vogt, 1948).

Acetylcholine is found in high concentration in the caudate and putamen of laboratory animals (MacIntosh, 1941), localized in nerve endings, specifically in synaptic vesicles (Lloyd and Hornykiewicz, 1970). The synthesizing enzyme, choline acetylase, and the inactivating enzyme, acetylcholinesterase, are similarly highly active in the striatum (Fahn and Côté, 1968). This high level of concentration for all three substances according to Hornykiewicz (1971) is equalled only by the concentration in the nuclei of the cranial motor nerves and motor nerve cells in the anterior horn of the spinal cord. Furthermore, the rate of acetylcholine synthesis in the caudate is high: Hebb et al. (1964) showed that in *in vitro* experiments on the caudate nucleus of the rat acetylcholine was synthesized at the rate of 8,000 to 10,000 µg.ACh per gm. tissue per hour, although the figures for *in vivo* synthesis are lower.

DOPAMINE

Like noradrenaline and adrenaline, dopamine is a naturally occurring catecholamine. Chemically, dopamine is β-3, 4-dihydroxyphenylethylamine or 3-hydroxytryamine. Pharmacologically, dopamine shares many of the peripheral actions of noradrenaline and adrenaline ; therefore it seems in general justified to classify dopamine as a sympathomimetic amine. Biochemically, dopamine formation represents the step immediately preceding the biosynthesis of noradrenaline. Small amounts of dopamine are found in all tissues where noradrenaline and adrenaline are produced (Hornykiewicz, 1971). Moreover, in addition to being the precursor of noradrenaline in the adrenergic neurone and of adrenaline in the chromaffin tissue, Blashko (1959) suggested, dopamine might have a physiological function of its own, and Carlsson (1959) envisaged the possibility of the central action of dopamine. Several workers since then (see e.g. Poirier, 1971; and Hornykiewicz, 1971) have demonstrated that dopamine satisfies many of the criteria of a physiologically active substance; it is now generally considered that dopamine fulfils two roles - one as the precursor of adrenaline and noradrenaline, and the other, as a neurotransmitter in its own right.

Metabolism and Turnover of Dopamine

Dopamine is formed from L-dopa, its immediate precursor, by the enzyme L-dopa decarboxylase. (L-dopa, in turn, is formed from tyrosine, by the enzyme tyrosine

hydroxylase). (see FIGURE 10). The reaction of L-dopa →

BIOSYNTHESIS AND METABOLISM OF DOPAMINE

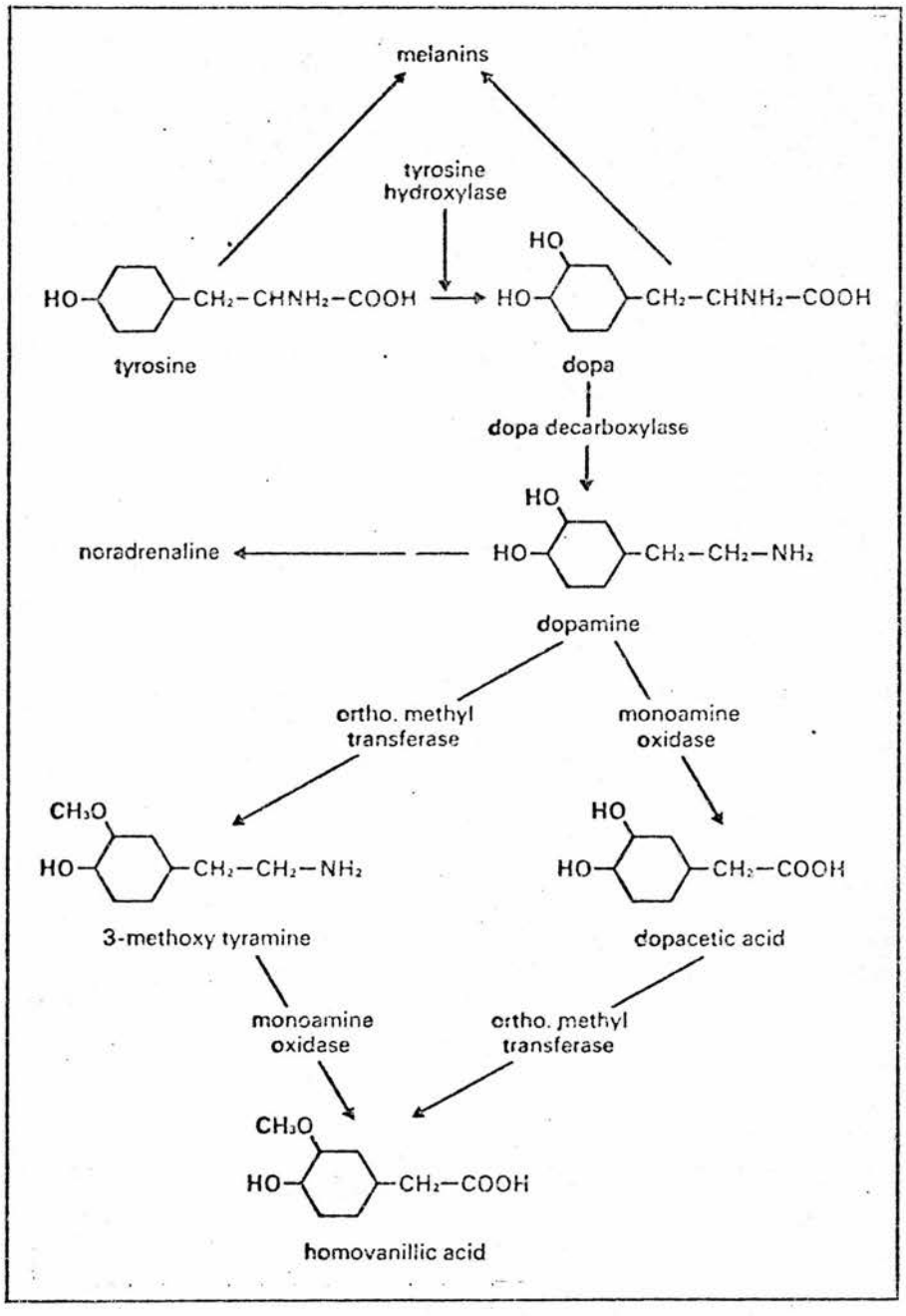



FIGURE 10

dopamine appears to be very efficient and to proceed at a considerable rate (Holtz, 1959). Although there is no strict correlation between the regional distribution of

the enzyme and the catecholamines in the brain (Hornykiewicz, 1966), it is clear that the highest enzyme activity is present in the caudate nucleus, the hypothalamus, and the mesencephalon (Bertler and Rosengren, 1959a; Bogdanskie et al., 1957; Holtz and Westermann, 1956). Levitt et al. (1965) have suggested that the limiting step in the biosynthesis of dopamine and noradrenaline might be the formation of L-tyrosine by the enzyme L-tyrosine hydroxylase. One would therefore not expect appreciable amounts of L-dopa to accumulate in brain tissue.

The relationship between dopamine and noradrenaline is interesting, but not yet fully understood. The studies by Glowinski et al. (1965) and Masuoka et al. (1963) demonstrated that in the striatum the metabolism for noradrenaline has quite different biochemical characteristics from that of dopamine. Furthermore, since in the caudate the activity of the enzyme dopamine-β-hydroxylase (responsible for the conversion of dopamine to noradrenaline) is high, one would not have expected Steg's finding (1964) that in spite of a high level of dopamine, noradrenaline is not formed at a commensurate rate. Hornykiewicz (1966) suggested two possible explanations for this finding: firstly, that the two amines may be localized in two separate structures within the striatum, and, secondly, that "either the dopamine and the enzyme are localized in separate compartments of the striatal cell or... there exists *in vivo* a lack of some factors necessary for full activity."

The main breakdown product of dopamine is homovanillic acid (4-hydroxy-3-methoxyphenylacetic acid, often abbreviated as HVA). This is aided by at least two enzymes: monoamine oxidase and catechol-O-methyltransferase (Axelrod, 1959). Dopamine is first attacked by monoamine oxidase, and 3,4-dihydroxyphenylacetic acid is produced. This compound, in turn, is O-methylated, and homovanillic acid is formed. However, Carlsson and Waldeck (1964) have shown that small amounts of dopamine may undergo O-methylation *before* oxidative deamination. The intermediary compound is 3-methoxytyramine. Its concentration increases considerably under the influence of monoamine oxidase inhibitors.

All available evidence indicates that brain dopamine is turned over at a high rate. Holzer together with Hornykiewicz (1959) injected harmine (a quick-acting MAO inhibitor) into rats, and found that within 10 - 20 minutes, there was a significant rise in the concentration of brain dopamine. Moreover, Undenfriend et al. (1958) suggested that this turnover of brain dopamine is comparable to that of brain 5-HT, but distinctly higher than that of brain noradrenaline. Vogt's observation (1954) of the occurrence of relatively high concentrations of HVA in the dopamine-rich parts of the brain and very low concentrations of the acid metabolites of noradrenaline, suggested that dopamine is turned over at a faster rate than brain noradrenaline. This hypothesis is further substantiated by Andén et al. (1964); Carlsson and Lindqvist (1962); and Laverty and Sharman (1965).

## Distribution of Dopamine in the Basal Ganglia

About 80 per cent of dopamine in the brain is distributed within the basal ganglia. (see FIGURE 11)

THE DISTRIBUTION OF DOPAMINE IN THE BRAIN

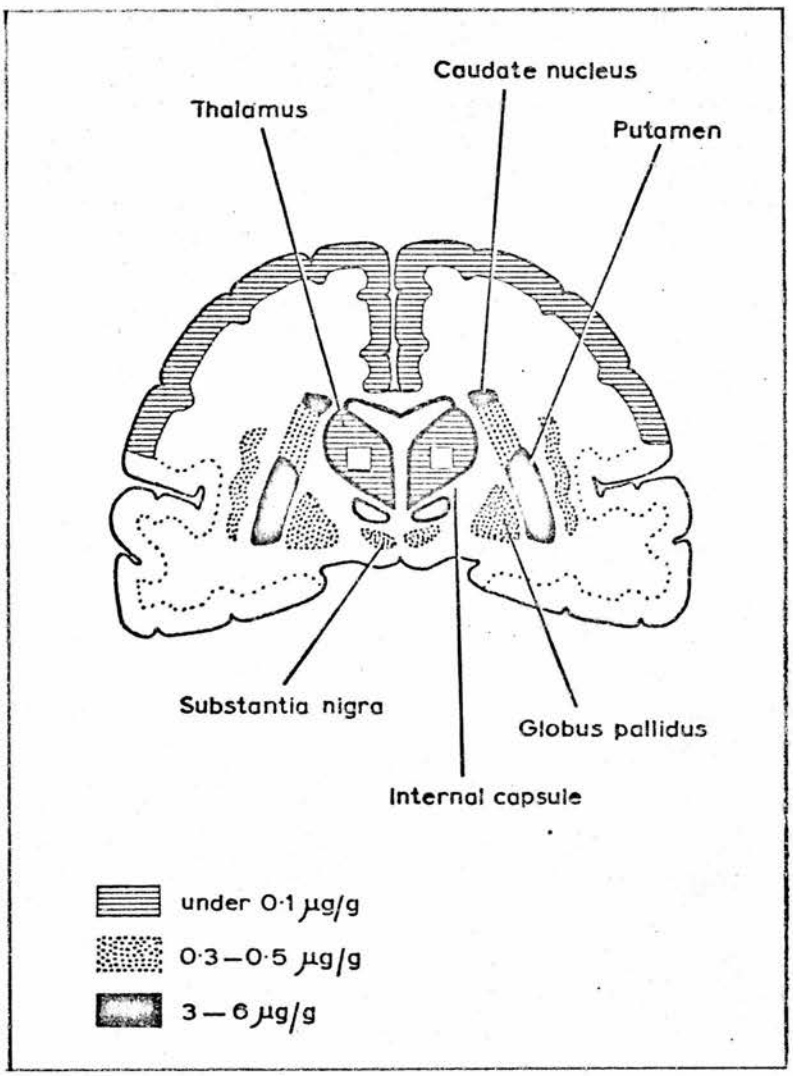



FIGURE 11

In 1959 it was shown, simultaneously by Carlsson and by Bertler and Rosengren that there is a regional

distribution of dopamine in the animal brain, with the highest concentrations of dopamine in the caudate nucleus and the putamen. Subsequently, Hornykiewicz (see Hornykiewicz, 1971) demonstrated that the compact layer of the substantia and the globus pallidus also have relatively high levels of dopamine. Bernheimer (1964) showed that homovanillic acid (HVA) has a characteristic distribution pattern similar to that of dopamine, with high levels in the caudate nucleus and putamen. However, in the substantia nigra there is a ratio of roughly 1:4 for dopamine and HVA, and in the globus pallidus a ratio of 1:25. Furthermore, Bertler and Rosengren (1959) found that throughout the internal capsule between the substantia nigra and striatum, there is an uneven, but identifiable, pattern of HVA distribution: the lowest concentrations were found in the caudal part, near the substantia nigra, and the highest concentrations in the anterior limb of the internal capsule close to the head of the caudate nucleus. Furthermore, noradrenaline and dopamine appear to have mutually independent areas of concentration: nuclei containing high levels of noradrenaline (such as the hypothalamus) are poor in dopamine, and nuclei rich in dopamine have low levels of noradrenaline (Carlsson, 1959; Bertler and Rosengren, 1959; Hornykiewicz, 1971). The distribution of amines within neural structures is summarized in TABLE 1.

DISTRIBUTION OF AMINES IN MAMMALIAN BRAIN[1,2]

| NEURAL STRUCTURE | AMINES | | | |
|---|---|---|---|---|
| | *ACh* | *DA* | *NA* | *5-HT* |
| olfactory bulb | 1300 | | | |
| neocortex | 2000 | | | 300 |
| hippocampus | | | | 900 |
| corpus striatum | 3000 | 9900 | | 700 |
| thalamus | 3000 | | 240 | 500 |
| hypothalamus | 1900 | 250 | 1000 | 1700 |
| central grey | | | 400 | |
| tegmentum | 1600 | 200 | 370 | 1000 |
| bulb | 1600 | | 350 | 600 |
| cerebellum | 200 | | | |

[1] *based on Adam (1969)*
[2] *mean estimates of concentration expressed as ng/g. Only concentrations <100 given.*

TABLE 1

## NEUROCHEMISTRY AND THE SUBCORTEX

### THE NIGRO-STRIATAL PATHWAY

There is strong evidence to suggest that there is a dopaminergic nigro-striatal pathway. Fuxe (1965) demonstrated that the neostriatum contains dopamine-containing axon terminals, and Dahlström and Fuxe (1964) showed that the neurones of the pars compacta of the substantia nigra were powerfully fluorescent. Furthermore, Andén et al. (1964) and Poirier and Sourkes (1965) found that nigral lesions caused a drop in the dopamine content of the ipsilateral striatum; Andén, Carlsson et al. (1964) and Andén, Dahlström et al. (1965) found ablation of the caudate nucleus produced an increased fluorescence

in the nigral neurones. Bédard et al. (1969) and Parent and Poirier (1969) have suggested that these dopaminergic fibres run in the medial forebrain bundle, and that there is a topographical relationship between the substantia nigra and the striatum.

Studies of the effects of iontophoretically applied dopamine and the effect of nigral stimulation on the caudate demonstrates clearly the function the dopaminerigc pathway subserves. Bloom et al. (1965), McLennan and York (1966), and York (1967) found that 60 to 70 per cent of cells whose activity was recorded were depressed by dopamine; and Albe-Fessard et al. (1967) and Connor (1968) found caudate nucleus cells (65 and 45 per cent respectively) were depressed by stimulation of the substantia nigra.

There is evidence to suggest that there are also nigro-striatal neurones with an *excitatory* function. Connor (1968), Feltz (1969), and Frigyesi and Purpura (1967), and McLennan and York (1967) have observed this effect in the caudate following electrical stimulation of the substantia nigra. A latency response (in cats) of 15 to 20 msecs. was usually found, indicating a possibility that the transmission is monosynaptic. Mettler, as early as 1945, suggested that there are axons arising not from the melanin-containing cells of the pars compacta, but from the pars reticulata, leading to the caudate. It is unlikely, therefore, that this excitatory connection between the substantia nigra and the caudate is, in fact, dopaminergic.

## THALAMO-CAUDATE PATHWAYS

The nucleus centrum medianum (CM) of the thalamus (and certain other medial nuclei) is possibly dopaminergic. Stimulation of the CM causes an increase in the dopamine output from the caudate (McLennan, 1964), and low-frequency repetitive stimulation of the CM inhibits firing of those neurones of the caudate which are depressed by dopamine (McLennan and York, 1967). The depressant actions both of CM stimulation and of dopamine application can be prevented by the iontophoretic application of phenoxybenzamine to the neurone under examination (York, 1967).

The ventral thalamo-caudate pathway in particular has been investigated by McLennan (1964) and McLennan and York (1966). Their studies provide strong evidence that there is a cholinergic mechanism in the pathway. Electrical stimulation of VA evokes an acetylcholine-release-response in the caudate; electrical stimulation of the caudate stimulates some neurones and inhibits others: both excitatory and inhibitory responses can be produced by iontophoretic application of acetylcholine to appropriate cells and these responses can be blocked by a cholinolytic agent.

## PUTAMEN

Dahlström and Fuxe (1964) demonstrated that the putamen possesses dopamine-containing neurones and, like

the caudate, has an abundance of histofluorescent terminals. A year later, in 1965, McLennan showed that electrical stimulation of the substantia nigra evokes a detectable release of dopamine from the putamen. York (1968, 1970) reported the effects of microiontophoretic application of dopamine upon the putamen. In the putamen, as in the caudate, a number of neurones were depressed by dopamine, but a significant proportion were excited. The neurones that were excited were those neurones that are capable of being activated by nigral stimulation. Both the chemically and electrically induced excitations were blocked by the application of dichloroisopropylnoradrenaline (nialamide). This evidence suggests that dopamine may function as an *excitatory* synaptic transmitter in the nigro-putamen pathway. According to McLennan (1971), "there is no inconsistency in the proposition that the same substance may act in one situation as an excitatory, and in another as an inhibitory, transmitter. Dopamine has been shown to act thus at certain of the ganglionic neurones of the mollusk *Aplysia*."

## STRIO-NIGRAL PATHWAYS

The major outflow from the striatum is to the pallidum, but there are also projections from the caudate and from the putamen to the substantia nigra. There is no pharmacological evidence, yet, on the striato-nigral connection, and hypotheses regarding the synaptic

mechanisms operating in the nigra are therefore based on indirect evidence.

In 1967, two studies were reported suggesting that the substantia nigra is neither morphologically nor physiologically homogeneous. Bak (1967) described two morphologically distinct synapse-types in the substantia nigra: one type contained the granulated vesicles characteristic of aminergic synapses, the other did not. Frigyesi and Purpura (1967) observed that stimulation of the caudate evoked in nigral neurones an excitatory post-synaptic response which was succeeded by an inhibitory response. These two findings indicate that two chemically distinct synaptic processes exist in the substantia nigra. Histochemical evidence supports this hypothesis. Localized in the zona reticulata of the substantia nigra is a profusion of very fine serotonin-containing terminals which establish contact with fibres of the "comb bundle". Fuxe (1965) found that these terminals and their connections exhibit cholinesterase stains, and Olivier et al. (1970) described the disappearance of this enzyme from the "comb bundle" fibres following striatal lesions.

## GLOBUS PALLIDUS

Evidence suggests that the pallidum is not dopaminergic. The pallidum itself does not contain large concentrations of dopamine (McLennan, 1963), nor does it have dopamine-containing nerve terminals (Fuxe, 1965).

There is, instead, evidence of serotonin-containing terminals (Fuxe, 1965), and of AChE being contained within the pallidal cells (McLennan, 1971). Malliani and Purpura (1967) suggested that either within the nucleus itself, or at the site of its projections, there is a dual transmitter system: they found that caudate stimulation evoked in pallidal cells an excitatory post-synaptic response followed by an inhibitory one.

## PALLIDAL AND THALAMIC PROJECTIONS

Pallidal fibres project to several thalamic nuclei: nuclei ventralis anterior (VA), ventralis lateralis (VL), and nucleus centrum medianum (Nauta and Mehler, 1966). In addition, afferents from the cerebellum passing through the brachium conjunctivum (Desivaju and Purpura, 1969) lead to certain VL neurones.

The biochemistry of the other pathways is more complex. Stimulation of the brachium conjunctivum produces a monosynaptic response in VL neurones which are strikingly cholinoceptive (Davis, 1966; McCance et al., 1968; McLennan et al., 1968). However, evidence indicates that the cerebellar efferents themselves are noncholinergic (McLennan, 1971). Although the excitability of VL neurones is reduced by dopamine and serotonin, noradrenaline has a complex effect. It excites a significant proportion of the cells and depresses others (Phillis and Tebécis, 1967). It has been suggested (McLennan, 1971) that "ACh and noradrenaline

act as synaptic transmitters in VL, respectively mediating the excitatory and inhibitory input to the cells from the mesencephalic reticular formation." Furthermore, since acetylcholine has been detected in pallidal neurones and some fibres of the ansa (McLennan, 1971) it may be supposed that the pallidal projections are cholinergic. Unfortunately, evidence to date does not support this view. Marshall and McLennan (unpublished observation, cited in McLennan, 1971) found "that atropine does not affect the electrical responses of the ventrolateral entopeduncularis"; and Fuxe (1965) did not find either serotonin- or catecholamine-containing terminals in the ventrolateral nucleus.

SUBCORTICAL PATHWAYS AND THEIR POSSIBLE TRANSMITTER SUBSTANCES[1]

| PATHWAY | | PROBABLE FUNCTION | POSSIBLE TRANSMITTER |
|---|---|---|---|
| *from* | *to* | | |
| striatum | pallidum | | acetylcholine |
| pallidum | VL, CM | excitatory | unknown (probably not ACh) |
| caudate | nigra | ? | acetylcholine; serotonin? |
| VA | caudate | excitatory | acetylcholine |
| VA | caudate | inhibitory | acetylcholine |
| CM | caudate | inhibitory? | dopamine |
| nigra | caudate | excitatory | unknown (but not DA) |
| nigra | caudate | inhibitory | dopamine |
| nigra | putamen | excitatory | dopamine |
| cerebellum | VL | excitatory | unknown (probably not ACh) |

[1]*based on McLennan (1971)*

TABLE 2

The distribution of monoamine connections between subcortical structures is summarized in TABLE 2.

# CHAPTER 3

# ASPECTS OF THE PATHOGENESIS OF PARKINSONISM

In this chapter evidence of the involvement of dopamine in the abnormal functioning of some of the basal ganglia is discussed. The hypothetical model of the pathogenesis of Parkinsonism based on this evidence has indicated a rational approach to treatment. Since the present investigation explores certain effects of L-dopa treatment in Parkinsonian patients, the question of treatment will also be considered.

## NEUROPHYSIOLOGICAL AND NEUROPATHOLOGICAL CONSIDERATIONS

Parkinsonism is characterized by a triad of motor symptoms - rigidity, tremor and akinesia. The neurophysiological mechanisms underlying these symptoms have not yet been established, but current theory holds that tremor and rigidity are 'positive' symptoms caused by an over-activity or release of certain brain areas. Since Parkinson's disease and post-encephalitic Parkinsonism are chronic and degenerative, Purdon Martin

(1959) pointed out that it is unlikely that there are so-called 'discharging' lesions in Parkinsonism. Instead, rigidity and tremor are considered to be 'release' symptoms, due to lack of an inhibition normally controlling excess of function, and resulting from destruction of some definite sub-cortical area or areas. Akinesia, on the other hand, is more properly considered a 'negative' symptom, and is, according to Denny Brown (1968), the "primary and fundamental" symptom of damage to the basal ganglia. But what of the lesion itself?

The most consistent neuropathological finding in Parkinsonism is the degeneration of the melanin-containing nerve cells in the zona compacta of the substantia nigra. (see FIGURE 12) Trétiakoff (1919) is often cited as providing the first important evidence of these changes. Greenfield (1955) summarized his work:

> Trétiakoff's important thesis (1919) was devoted almost entirely to the substantia nigra. This was examined in fifty-four cases of various kinds, including nine typical long-standing cases of paralysis agitans and three of encephalitis lethargica, which was at that time a new disease. In the latter he found a concentration of inflammatory lesions in the substantia nigra, where most of the nerve cells had disappeared and many of those which remained had undergone hyaline or granular degeneration. This is one of the earliest references to the destruction of the substantia nigra in encephalitis lethargica, a lesion which was to have a profound influence on later theories of the pathology of idiopathic Parkinsonism. In his cases of the latter type he found a varying degree of cell-loss in the substantia nigra. Various changes were seen in the remaining neurones, the most important being grumous degeneration (dégénérescence gruméleuse), neurofibrillary alterations, Lewy's spherical hyaline inclusions and bi-nucleation. Lewy's inclusions were found in six of his nine cases of typical paralysis agitans and in one atypical case. After a full review of the literature he expressed the opinion that the substantia nigra was constantly

High power photomicrographs to illustrate loss of pigmented cells in the substantia nigra in a Parkinsonian brain.

normal Parkinsonian

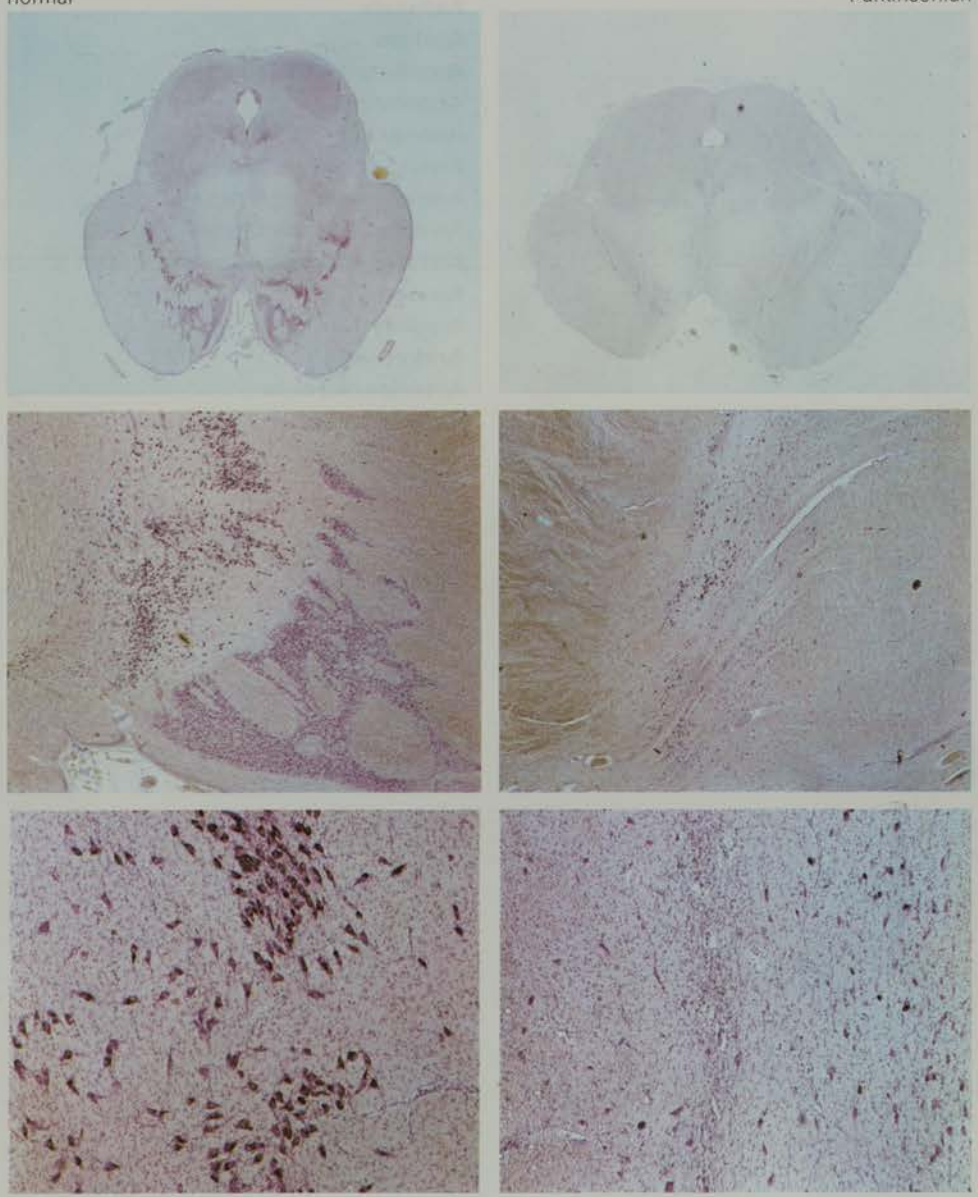


FIGURE 12

affected, but that the lesions in it were always associated with other senile lesions. In no case could he find any lesions in the nucleus ruber.

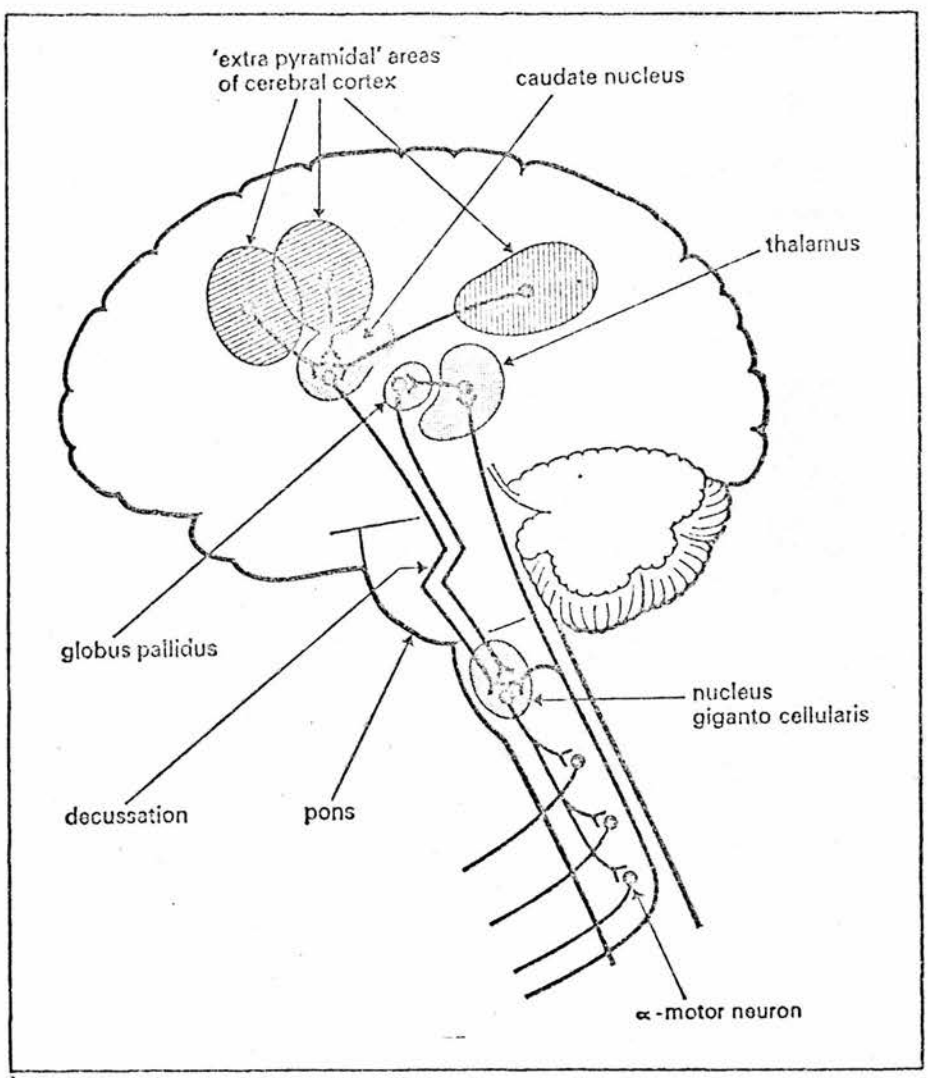
Hassler (1938, 1953), Foix and Nicolesco (1925), Greenfield and Bosanquet (1953), and Jung and Hassler (1960) have confirmed Tretiakoff's findings, but Hassler (1953) expressed the view that the observed degenerative changes in other sub-cortical nuclei are probably irrelevant to the Parkinsonian symptomatology. It is not at all clear in which way degeneration of the substantia nigra induces functional changes in other subcortical nuclei to produce the characteristic Parkinsonian symptomatology. There are, however, plausible hypotheses of symptom-production.

## RIGIDITY AND TREMOR

Denny Brown (1969) argued most persuasively the case for considering rigidity and tremor as different aspects of one pathogenesis. ("[Each is] ... a conflict of released proprioceptive reaction. The conflict is released more slowly in rigidity, and more rapidly and rhythmically in tremor..."). Destructive lesions of the pre-motor cortex, basal ganglia, mid-brain or cerebellum in primates have been used, to a large extent, as a basis for models of rigidity. It is now generally accepted that the final common pathway for dystonia is the $\alpha$-motor neurone rather than the $\gamma$-efferent, and that there is a tendency towards flexor muscles being more

involved, accounting, to some extent, for the flexed posture of Parkinsonian rigidity (Denny Brown, 1960a, 1960b). The cells of this final common pathway are situated centrally, in the gigantocellular nucleus of the the medulla (Denny Brown, 1968). Destruction of this descending pathway results in a facilitation of its output to the α-motor neurones of muscles (particularly the flexors). Thus, when it is sustained, the augmented activity results in rigidity and the flexed dystonic posture of Parkinsonism; when it is interrupted the characteristic Parkinsonian tremor results. (see FIGURE 13)

DIAGRAM TO ILLUSTRATE THE PHYSIOLOGY OF DYSTONIA[1]




[1]*after Denny-Brown (1969)*

FIGURE 13

Hornykiewicz (1966), arguing from surgical evidence showing that destruction of the pallidum or its ventrolateral thalamic projections make rigidity and, to a lesser extent, tremor, disappear, suggested a pathogenesis for dystonia which complements rather than challenges Denny Brown's theory. Hornykiewicz postulated that "some inhibitory effect, normally suppressing an excess of activity of the pallidum, is removed by degeneration of the substantia nigra, and that this results in rigidity. Probably this nigral inhibition of pallidal activity is mediated by nigro-pallidal fiber connection....."

AKINESIA

To account for the relation between degeneration of the substantia nigra and akinesia, Hassler (1953) proposed that some of the facilitatory motor impulses originating in the cortex are relayed via the substantia nigra to the motor neurones, thus enhancing the spontaneous movement. However, in addition to Hassler's direct descending facilitatory influence, the substantia nigra, through its intimate connection with the striatum, is able to exert a second, and indirect, influence on motor impulses.

Hornykiewicz has pointed out (1966) that there are two equally plausible forms this indirect influence can take, and each is equally supported by neurophysiological and neuropathological evidence. On the one hand, it

could be postulated (on the basis of Jung and Hassler, 1960) that the striatum has a *depressant* effect on spontaneous activity, and that the substantia nigra in inhibiting this depressant effect, enhances activity. On the other hand, it could be postulated (on the basis of Spiegel, 1964; Spiegel and Szekely, 1961) that the striatum acts to *enhance* activity, and in this case that the substantia nigra reinforces this enhancement by stimulating the striatum. In either case, destruction of the substantia nigra would lead to decreased ability of the individual to perform spontaneous voluntary movements.

## NEUROCHEMICAL CONSIDERATIONS

Following the discovery in 1958 of a regional distribution of dopamine in the animal brain (see Chapter 2), it was suggested that dopamine might be involved in the functioning of the basal ganglia, and in such disorders as Parkinsonism. Carlsson and his co-workers (1971) set forth their hypothesis and the evidence in its favour as follows:

> The corpus striatum forms an important part of the extra-pyramidal system, which is known to control motor activity. Lesions in this system are accompanied by different kinds of kinetic disorders. Thus the parkinsonian syndrome is characterized by slowing and enfeeblement of emotional and voluntary movement, muscular rigidity, and tremor. Chorea, on the other hand, presents features which are in some respects the opposite of the symptoms of parkinsonism, with involuntary movements and, frequently, emotional instability. It is

interesting to note that reserpine, which depletes dopamine from the corpus striatum, may produce a syndrome very similar to parkinsonism and appears to be efficient in controlling the choreatic syndrome.

Thus the following facts argue for the assumption that dopamine is involved in the control of motor functions:

1. The presence of large amounts of dopamine in the corpus striatum, which forms an important part of the extrapyramidal system.
2. The extrapyramidal actions of reserpine, which depletes dopamine from the corpus striatum.
3. The ability of DOPA to counteract the hypokinetic action of reserpine. Whether this action of DOPA is entirely due to formation of dopamine, or whether formation of noradrenaline contributes to the effect, remains an open question (Carlsson, 1971).

Extensive study of the behaviour of this biogenic amine in the human brain, and particularly in the brain of Parkinsonian patients, followed publication of this hypothesis. Hornykiewicz has been in the forefront of these clinical studies and his contribution to the neurochemistry of Parkinsonism cannot be overestimated. He, together with co-workers, has shown that in Parkinsonism the concentration of dopamine is decreased to very low levels in the caudate nucleus, putamen (Bernheimer et al., 1963; Ehringer and Hornykiewicz, 1960), and substantia nigra (Hornykiewicz, 1963). (see TABLE 3) He has also shown that the concentration of homovanillic acid in these areas, as well as in the globus pallidus and all portions of the internal capsule between the substantia nigra and the striatum, was significantly reduced (Bernheimer and Hornykiewicz, 1965; Hornykiewicz et al., 1968). The observations of the concentrations of homovanillic acid are important, for as Hornykiewicz (1971) pointed out, "they rule out

the possibility that the low dopamine levels in parkinsonism could be due to postmortem breakdown of this rather labile amine, since homovanillic acid is a perfectly stable compound under postmortem conditions." Moreover, as Bernheimer et al. (1963) have shown, in Parkinsonian patients treated with a monoamine oxidase inhibitor, the striatal dopamine was approximately as low as in untreated cases.

BIOCHEMICAL FEATURES OF PARKINSON'S DISEASE[1]

| BRAIN AREA | DA µg/g. | | NA µg/g. | | 5-HT µg/g. | |
|---|---|---|---|---|---|---|
| | *normal* | *Parkinson* | *normal* | *Parkinson* | *normal* | *Parkinson* |
| cortex | 0.00 | - | 0.03 | - | 0.04 | - |
| caudate | 3.50 | 0.32 | 0.07 | 0.03 | 0.33 | 0.12 |
| putamen | 3.57 | 0.23 | 0.11 | 0.03 | 0.32 | 0.14 |
| pallidum | 0.30 | 0.14 | 0.09 | 0.11 | 0.23 | 0.13 |
| thalamus | 0.01 | 0.01 | 0.09 | 0.05 | 0.26 | 0.13 |
| hypothalamus | 0.02 | 0.00 | 1.29 | 0.67 | 0.29 | 0.12 |
| nigra | 0.46 | 0.07 | 0.04 | 0.02 | 0.55 | 0.26 |

[1]*based on Hornykiewicz (1964).*

TABLE 3

Although there is generally a more marked dopamine deficiency in the post-encephalitic form of Parkinsonism, as compared to the idiopathic paralysis agitans form, (Bernheimer et al., 1965; Ehringer and Hornykiewicz, 1960) this difference is not absolute. Indeed, regardless of the clinical and pathological classification of the examined cases, a correlation between the degree of cell loss in the substantia nigra and the degree of dopamine and homovanillic acid deficiency has been shown (Bernheimer et al., 1965). A group of workers in France

(Sharman et al., 1967), using animals with experimental nigral lesions, confirmed this correlation. An unpublished study by Hornykiewicz and colleagues[1] of chronic manganese poisoning in a patient with Parkinson-like symptoms showed not only degeneration of nerve cells particularly of the substantia nigra, but also very low concentrations of dopamine in the striatum. From this type of data Hornykiewicz (1971) drew the following important conclusion:

> This indicates that there is no direct connection between the etiology of parkinsonism and the neurochemical changes. On the contrary, it can be postulated that, regardless of the etiology, parkinson-like symptomatology can be expected in all instances following cell loss in the substantia nigra and the subsequent abnormally low levels of dopamine and homovanillic acid in the striatum.

Logically, findings such as these suggest Parkinsonism should be considered a "striatal dopamine deficiency syndrome" (Hornykiewicz's terminology - see Hornykiewicz, 1970). But *do* the neurophysiological and clinical observations, in fact, correlate with this neurochemical implication?

As has been discussed in Chapter 2, not only has the nigro-striatal tract been demonstrated, but it has also been shown that neurones of the zona compacta of the substantia nigra which contain dopamine have axons ascending ipsilaterally in the internal capsule to terminate (after penetrating the globus pallidus) in the caudate nucleus and in the putamen. Data such as that

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[1]cited in Hornykiewicz (1971).

presented in TABLE 3 could thus be explained by a lesion anywhere along this tract. The biochemical connection is more than inferential, for depletion of dopamine in the striatum has been shown to follow lesions which interrupt the nigro-striatal tract between the cell body and the nerve terminals (Andén et al., 1964; Dahlström and Fuxe, 1964; Poirier and Sourkes, 1965). Furthermore, Hornykiewicz and colleagues (Ehringer and Hornykiewicz, 1960; Bernheimer et al., 1965) have demonstrated that the deficiency of dopamine (and HVA) in the striatum of Parkinsonian patients is well correlated with the degree of cell-loss of the pars compacta of the substantia nigra.

Clinically, "one of the best examples" (Hornykiewicz, 1971) illustrating the causal relationship between striatal dopamine deficiency and Parkinsonian symptomatology is demonstrated in a study (Barolin et al., 1964) of a patient with hemi-Parkinsonism. In this patient, dopamine deficiency was much more pronounced in the striatum contralateral to the side of the symptoms, although striatal dopamine ipsilateral to the symptoms was 'subnormal' (see TABLE 4). Moreover, similar changes in dopamine concentrations are not found in other basal ganglia disorders. Patients dying from Huntington's chorea with advanced atrophy of the caudate nucleus were shown (Bernheimer et al., 1965; Ehringer and Hornykiewicz, 1960) to have normal dopamine concentrations in the remaining striatal tissue.

CONCENTRATION LEVELS OF DOPAMINE AND SEROTONIN IN THE STRIATUM OF A RIGHT-SIDED HEMIPARKINSONIAN PATIENT.[1]

| | DOPAMINE (µg/gm.) | | SEROTONIN (µg/gm.) | |
|---|---|---|---|---|
| | *normal* | *hemiparkinson (right side)* | *normal* | *hemiparkinson (left side)* |
| Caudate nucleus | | | 0.33 | |
| right side | 3.28 | 1.25 | - | 0.26 |
| left side | 3.55 | 0.59 | - | 0.26 |
| Putamen | | | 0.32 | |
| right side | 3.73 | 0.93 | - | 0.26 |
| left side | 4.74 | 0.13 | - | 0.21 |

[1]*based on Hornykiewicz (1971).*

TABLE 4

It is, therefore, reasonable to hypothesise that in Parkinson's disease the typical neuropathological changes with degeneration of the substantia nigra produce degeneration of the nigro-striatal tract and its termination in the striatum with resulting depletion of striatal dopamine. This hypothesis provides the basis for a model describing the striatum as a higher regulatory centre: dopamine chemically transmits nigral impulses inhibiting activity of the pallidum and nigral impulses inhibiting (or enhancing) activity of the caudate nucleus.

## PHARMACOTHERAPEUTIC CONSIDERATIONS

In 1961, two independent groups of workers tested

this hypothesis by replenishing the striatal dopamine. Barbeau, Sourkes and Murphy in Montreal gave doses of 300mg. Laevodopa orally and found there was a significant reduction in rigidity, with no effect on tremor. Birkmeyer and Hornykiewicz in Vienna administered up to 150mg. Laevodopa intravenously to their patients and found a "complete abolition or substantial decrease of akinesia". Birkmeyer and Hornykiewicz were much impressed by the efficacy of Laevodopa. They stated that a qualitatively similar effect "could not be achieved to any comparable degree by any other known drug."

Unfortunately, the unpleasant side-effects of intravenous Laevodopa (particularly nausea, vomiting and fluctuation in blood pressure) "made it practically impossible to inject doses that were large enough to increase the dopamine sufficiently in the striatum" (Ehringer and Hornykiewicz, 1960). The publication in 1967 by Cotzias, Van Woert and Schiffer of results of a study of patients given high oral doses of D,L-Dopa suggested a possible solution. They showed that by starting with low doses (approximately 0.3gm daily), and gradually increasing the dose over several weeks to about 6gm daily, it was possible not only to obtain maximum beneficial responses, but also to overcome several of the side-effects. The racemic D,Lcompound, however, proved sufficiently toxic to limit its use: large doses could not, with safety, be adminstered to the mildest cases (Cotzias et al., 1967).

In another study, Cotzias and colleagues (1969)

attempted to overcome this difficulty. Instead of the racemic D,Lcompound, they used the amino acid precursor dihydroxphenylalanine (dopa) - the amine previously used (intravenously) by Birkmeyer and Hornykiewicz (1961), and (in small oral doses) by Barbeau et al. (1962). It was administered (as D,L-Dopa had been administered in the previous study) *orally, in gradually increasing doses.* Cotzias insisted that this gradually increasing dose regime is of extreme importance: "... the optimum dose was reached no sooner than after five to seven weeks. We cannot over-emphasize the importance of slow increments and of slow mobilization of these individuals. The optimum dose was the daily dose which induced maximal improvement with minimal side effects.... It varied between 4 and 8g. per patient per day." The results of the study were highly favourable. L-dopa was shown to have positive effects on the akinesia of Parkinsonism. Moreover, Cotzias' study demonstrated not only that large doses of L-dopa are needed and that these must be gradually built up, but also that treatment must be prolonged, and that unlike intravenous Laevodopa, oral Laevodopa does not produce an immediate effect.

At a conference in Geneva, Barbeau (1970 ) reviewed his own experience with L-dopa as a treatment for Parkinsonism, and showed that over the years the initial and highly favourable opinion Birkmeyer and Hornykiewicz had formed from their pioneering work with intravenous L-dopa in 1961, has been justified:

Ten years of experience with L-dopa have clearly shown that this drug is by far the most useful treatment presently available for Parkinson's disease. It is effective against all major aspects of the illness, but not equally so. Hypokinesia, or akinesia, is the first symptom to be reversed, sometimes completely. Speed in the initiation of movements, associated movements, postural balance are all impaired in this syndrome and are uniformly and rapidly improved with Dopa.... On the other hand, other symptoms are not always completely reversed by treatment. Rigidity is decreased in most cases but can reappear after some months. Tremor is usually not modified appreciably until after 2 or 3 months of continued therapy. In the first weeks of L-Dopa, tremor can even be temporarily increased. These observations would indicate that the effect of L-Dopa on akinesia is a direct one, while that on rigidity and tremor involved secondary and less specific mechanisms of action.

How does Laevodopa produce this effect? It is clear that the effect cannot be due to L-dopa itself, for the amine proved to be relatively inactive (Carlsson, 1971). There is sufficient evidence to consider the central nervous system as the site of the action (see Hornykiewicz, 1970). Any of the numerous central metabolites of L-dopa could be the active compound, but dopamine, serotonin, and noradrenaline, have suggested themselves as more likely candidates. Although it is not feasible to identify conclusively one of the three as the decisive compound, experimental evidence suggests that the anti-Parkinsonian action is dopamine-dependent. Birkmeyer and Hornykiewicz (1961), for example, on the basis of an extensive clinico-pharmacological study, showed dopamine formed in the brain from (in this case, intravenously administered) Laevodopa to be the critical amine. Additional support is given to this claim by their report (corroborated by Barbeau et al., 1962) that

the effect of Laevodopa can be increased five-fold if patients are pre-treated chronically with a monoamine inhibitor. Hornykiewicz, in a paper (1970) presented to a conference in Quebec, summarised current views on the anti-Parkinsonian effect of L-dopa. Although the paper was read some years ago, no evidence has been published since to gainsay his conclusions:

> In spite of several questions which will remain open..., it seems that at the moment the anti-parkinsonian action of L-dopa is best explained by assuming that it is the *dopamine formed in the brain* which is the active compound, and that there is a close relationship between striatal dopamine deficiency and parkinsonian akinesia and rigidity. This evidence is in keeping with a large body of fairly solid evidence obtained in animal experiments, especially in respect of striatal dopamine metabolism in reserpined animals and Dopa-reserpine antagonism. Therefore, it would appear that, for the time being, we are justified to say that in principle we have a rational basis for the use of L-dopa in parkinsonism.

If one accepts this hypothesis that *dopamine* formed in the brain from L-dopa is the active substance, how can the therapeutic action be accounted for? In the literature many suggestions, of varying plausibility, are to be found. For example, a recent publication ( Anon. , 1970) included in its list of "main possibilities" the following:

Treatment with L-Dopa may result in the increase of extrastriatal dopamine. Concentrations of dopamine throughout the central nervous system might have a specific neurohormonal effect in the striatum and tend to counteract the depletion of intraneuronal dopamine resulting from the disease.

The metabolism of the nigro-striatal neuron is distrubed in such a way that the rate of dopamine production is defective. If this were the case, as Cotzias has suggested, treatment with L-Dopa acts by "saturating an enzyme with substrate." The degeneration of the nigral

neurons may come about either as a secondary phenomenon or may be primary and causative of the defective dopamine production.

Suggestions such as these, unfortunately, are open to criticism as naïve, reductionistic extrapolations from limited premises. Not only is the dopaminergic system treated in isolation, but emphasis is given to absolute levels of amine concentration. This is perhaps not the most profitable approach, as the development of serotonin theories in Parkinsonism indicates.

Postmortem studies on Parkinsonian patients showed that in addition to the dopamine depletion, there is also a serotonin depletion (see, for example, TABLE 3). One study found that serotonin levels in the striatum, globus pallidus and substantia nigra were as much as 50% lower in Parkinsonian patients than in controls (Bernheimer et al., 1963). In spite of experimental findings (Poirier et al., 1969a)suggesting a connection between 5-hydroxytryptamine and 'positive' Parkinson-like symptoms in monkeys, serotonin depletion was not generally considered to be a characteristic or specific Parkinsonian feature:

> 1) Taking into consideration the wide range of values obtained in human postmortem material, the decrease in brain serotonin in parkinsonism was mild as compared with the severe dopamine deficiency found in the same patients. 2) A patient ... with hemi-parkinsonism did not show a preferential decrease of striatal serotonin contralateral to the side of the symptoms. 3) In parkinsonian patients treated chronically with monoamine inhibitors, the brain serotonin was markedly elevated to above-normal levels, whereas striatal dopamine remained virtually unchanged. In these patients the clinical action of monoamine oxidase inhibitors on the parkinsonian symptoms was very mild and not always consistent.

4) Increasing brain serotonin in parkinsonian patients by giving its precursor 5-hydroxytryptophan had no beneficial effect on the chief symptomatology of the disorder (Hornykiewicz, 1971).

If, however, the focus of attention is moved away from *absolute* levels of one particular amine, more powerful and, intuitively, more plausible hypotheses are possible. Hassler and Bak (1969), in particular, have argued strongly that it is not the absolute amounts of serotonin, but rather the *ratio* of serotonin to dopamine in the striatum that is critical.

If the content of serotonin in the striatum of the rat is increased by administration of drugs such as harmaline, rigidity and tremor-like jerks occur. If, on the other hand, the dopamine content of the striatum is increased by intra-peritoneal administration of a monoamine oxidase inhibitor such as iproniazid to block the deamination of dopamine along with L-DOPA the rats become hyperactive.

When a rat has undergone hemidecerebration (which can be accomplished functionally by the brain incision... which interrupts the fibres connecting the striatum and the substantia nigra) slight contralateral tremor and ipsilateral circling are seen, along with a 50 per cent decrease in dopamine in the isolated striatum but with no change in serotonin content. The tremor can be amplified by increasing the striatal serotonin with harmaline. On the other hand, combining hemidecerebration with an increase of dopamine, by the administration of L-DOPA and iproniazid, results in extremely high jumping to the point of exhaustion. More detailed study of this correlation reveals than an increase in either dopamine or serotonin is not associated, in most cases, with a decrease of the other or of other substances.

Both the animals with increased striatal serotonin and normal dopamine (after harmaline administration) and the animals with decreased dopamine but normal serotonin (hemidecerebrated) exhibit tremor.

This is the first demonstration that it is not the absolute value of serotonin which may be responsible for this motor activity, but the ratio between dopamine and serotonin. If the ratio becomes smaller than unity rigidity and tremor-like myoclonus appear, regardless of the means by which this ratio is altered, whether by a simple hemidecerebration or by drug administration. If, of the contrary, the dopamine in the striatum is increased relative to the serotonin the rats become hyperactive and

start to jump. In each case a relative increase of dopamine in relation to serotonin causes hyperactivity and a relative decrease of dopamine in relation to serotonin gives rise to rigidity and tremor-like movements. If in hyperactive, exophthalamic, jumping rats the dopamine-to-serotonin ratio is reversed by harmaline administration to a value of less than unity the motor symptoms are also reversed. Only the ratio of these two amines in the striatum is crucial for the motor effect.

The biochemistry of mental disorders is a rapidly growing area, and of late the dopaminergic system has received increasing attention. However, Barbeau (1972), although careful not to suggest an alternative to Brodie's "serotonin hypothesis" and to Schildkrant's "noradrenaline hypothesis" of depression, does draw attention to the role of dopamine in Parkinsonian depression. Some drug-induced depressions have been reversed with L-dopa (but see Barbeau, 1972); and there is an "apparent reversal of the state of depression (at least the 'reactive' component) in most, but not all parkinsonian patients treated with L-dopa" (Barbeau, 1969). The implicit relationship between dopamine and serotonin in Parkinsonian depression adds further weight to the importance of taking a more global view of the biochemical aspects of the disease.

The amine-ratio suggested by Hassler and Bak, and evidence such as that discussed above concerning the function of serotonin, are highly pertinent to aspects of the pathogenesis and treatment of Parkinsonism, but this line of approach has not yet been fully explored. Hornykiewicz considered serotonin not to be a critical

amine since, among other reasons, increasing serotonin concentration levels did not reduce the *symptoms* of the disease. Hassler and Bak's work, however, suggests that if the *serotonin - dopamine ratio* is reduced gross hyperactivity develops. The relevance of the serotonin - dopamine *ratio* to the hyperkinetic side-effects in some patients from dopamine therapy has *not* been tested. If this relationship were supported experimentally, one would possibly be able to explain why patients develop these side-effects, and an alternative means of treatment, which would not necessitate reduction of dopamine therapy with the consequent sacrifice of efficacy of treatment, would be available.

This type of amine equilibrium hypothesis has been used before. The hypothesis that Parkinsonian akinesia and rigidity are due to disequilibrium between antagonistic monoaminergic (MA) and cholinergic (ACh) neurone systems was advanced by Barbeau (1962). Under normal physiological conditions a delicate functional equilibrium exists between the excitatory cholinergic and the inhibitory dopaminergic mechanisms within the striatum which enable it to function as a higher regulatory centre for subcortical ('extra-pyramidal') motor activity. In Parkinsonism, depletion of dopamine reduces the inhibitory influence, and allows excessive cholinergic effects. (see FIGURE 14)

The hypothesis is well supported by several clinical and neuropharmacological observations. For example, it

is well known that physostigmine and other centrally acting cholinergic drugs significantly aggravate Parkinsonian symptoms (Duvoisin, 1967). In animals reserpine (which depresses MA activity and depletes striatal dopamine) produces striking Parkinson-like symptoms (Carlsson et al., 1958). Moreover, L-dopa injected into such reserpine-treated animals restores (albeit transiently) the striatal dopamine levels and reverses all the symptoms induced by reserpine (Carlsson et al., 1957). In man, L-dopa has been shown to counteract several signs of reserpine action (Degwitz et al., 1960).

THE DISEQUILIBRIUM HYPOTHESIS OF PARKINSONISM

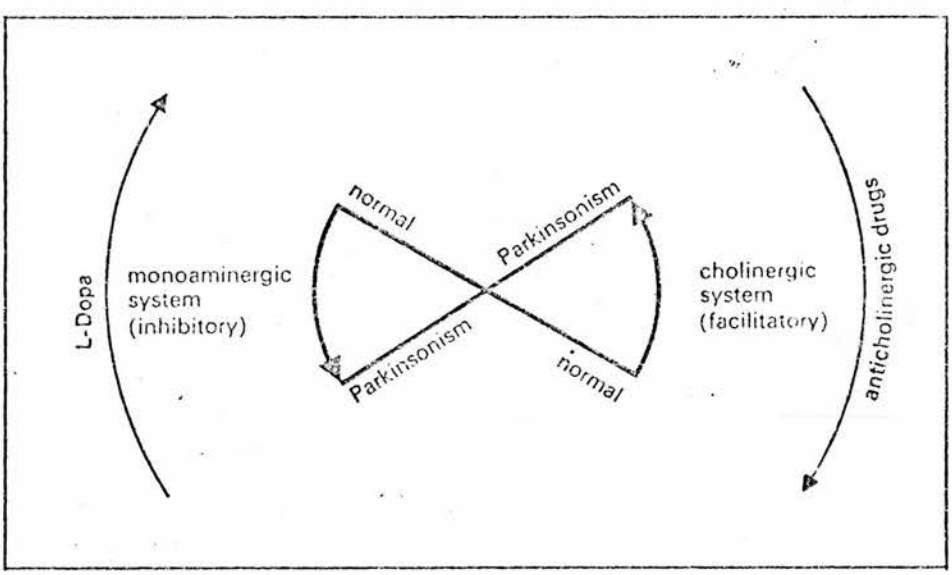



FIGURE 14

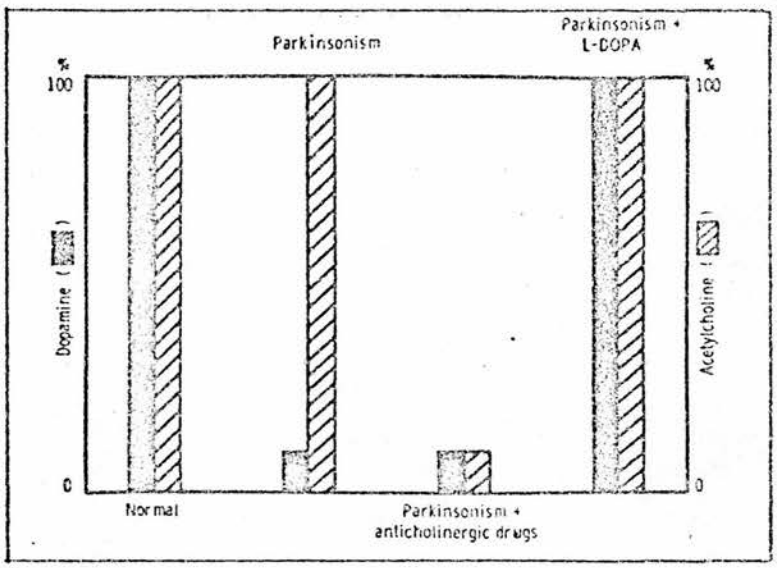
On the basis of experimental analysis of drug-induced akinesia and rigidity in animals, Steg (1969) has extended the disequilibrium hypothesis of Parkinsonism into an extremely interesting and plausible neurophysiological model linking peripheral and central mechanisms:

The central nervous system controls the muscles via the α- and γ-efferent systems. The contraction of the skeletal muscle is controlled directly from the α-motoneurones. The γ-motoneurones innervate the muscle spindles and regulate the muscle length via monosynaptic stretch reflex arc. Normal motor function requires the participation of both of these routes of efferent muscle control. Reserpine and physostigmine increase the α- and decrease the γ-motoneurone activity simultaneously with the appearance of akinesia and rigidity. L-DOPA and atropine respectively abolish the akinesia and rigidity and restore the normal balance between the α- and γ-motoneurone activity.... It is suggested that the rigidity is due to α-motoneurone hyperactivity and that the akinesia is due to γ-motoneurone hypoactivity.

The hypothesis of functional disequilibrium in Parkinsonism is helpful. It emphasises the inter-relationships of the biogenic amines and it provides a useful model for explaining the beneficial effects of the major anti-Parkinsonian drugs presently in clinical use. Anticholinergic drugs are efficacious because they decrease the relative predominance of cholinergic activity in the striatum and hence restore the dopamine - cholinergic balance. L-dopa therapy, on the other hand, raises the dopamine level till it balances the excessive cholinergic level. It is clear that in these two cases equilibrium is reached at different amine concentration levels: the anticholinergic drugs can restore equilibrium at much lower than normal levels, and L-dopa which theoretically 'normalizes' striatal dopamine establishes equilibrium at approximately the normal level. Thus it can be expected that both anticholinergic and dopaminergic drugs will exert a beneficial effect and reduce Parkinsonian symptomatology, and that dopaminergic drugs will be far more effective than the relatively

weaker anticholinergics. (see FIGURE 15) Furthermore, one would predict that the anticholinergic drugs, in controlling the activity of the striatal cholinergic mechanism, would have an observable effect on rigidity and tremor, whereas dopaminergic drugs, in correcting the basic dopamine deficiency, would primarily affect akinesia. And, as is apparent from preceeding discussion, clinical evidence supports this pharmacotherapeutic hypothesis.

COMPARISON OF DOPAMINERGIC AND CHOLINERGIC DRUGS[1]




[1]*from Hornykiewicz, 1971.*

FIGURE 15

# CHAPTER 4

# SPEECH DISORDERS AND PARKINSONISM

## A REVIEW OF LITERATURE FROM 1817 TO CIRCA 1960

### SPEECH DISTURBANCE IN PARALYSIS AGITANS

"Paralysis agitans" was first described by a London physician, James Parkinson, in his monograph *An Essay on the Shaking Palsy* (1817). Parkinson's writings show him to be a man of astute observation and methodical approach. Throughout his monograph he collated his observations and drew parallels between his patients' symptoms thus providing concise summaries of salient features of the disease.

James Parkinson recognized disturbances of speech to be an important feature of the disease which now bears his name. The disturbances manifest themselves with the passage of time and the concomitant progression of the disease. Once the disease has progressed to involve both halves of the body, Parkinson observed, both speech and the intimately associated vegetative functions are impaired. This observation is of central importance in Parkinson's formulation of a hypothesis concerning the

site of the responsible lesion. Although his actual location of the lesion has since been shown to be inaccurate, the logical sequence through which he worked can hardly be faulted.

> By the nature of the symptoms we are taught, that the disease depends on some irregularity in the direction of the nervous influence: by the wide range of parts which are affected, that the injury is rather in the source of this influence than merely in the nerves of the parts; by the situation of the parts whose actions are impaired, is the order in which they become affected, that the proximate cause of the disease is on the superior part of the medulla spinalis; and by the absence of any injury to the senses and the intellect, that the morbid state does not extend to the encephalon...
>
> From the impediment to speech, the difficulty in mastication and swallowing, the inability to retain, or freely eject, the saliva, may with propriety be inferred an extension of the morbid change upwards through the medulla spinalis to the medulla oblongata, necessarily impairing the powers of several nerves derived from that portion into which the morbid change may have reached.

The nature of the speech disturbances are not particularly well described by Parkinson himself. He wrote of one patient's words being "scarcely intelligible"; of cases 2 and 6 having their speech "interrupted"; and with reference to another patient, he referred to the "impediment to speech". He did, however, include in his monograph the full and descriptive case notes of the Count de Lordat, which were written by Dr. Maty. It is from these notes that a clear picture of advanced Parkinsonian dysarthria emerges. Take, for example, this passage:

> What words he still could utter were monosyllables, and these came out, after much struggle, in a violent expiration, and with such a low voice and indistinct articulation as hardly to be understood but by those who were constantly with him... his senses, and the powers of his mind [were] unimpaired; he was attentive to,

and sensible of everything which was said in conversation, and showed himself very desirous of joining in it; but he was continually checked by the impediment in his speech, and the difficulty which his hearers were put to.

To his colleague's excellent description Parkinson added one important feature - the temporal disturbance, "festination". Parkinson was not the first to observe festination *per se*. He himself credits de Sauvage with the term "festination" and Gaubius with being the first to observe and describe the phenomena of hurried talking and walking. In his monograph, Parkinson provided the following translation of a key passage from Gaubius' writing:

Cases occur in which the muscles duly excited into action by the impulse of the will, do then, with an unbidden agility, and with an impetus not to be repressed, accelerate their motion, and run before the unwilling mind. It is a frequent fault of the muscles belonging to speech, nor yet of these alone: I have seen one, who was able to run, but not to walk.

At the time when Parkinson's monograph was published, festination was considered a syndrome in its own right. Parkinson, however, had noted sufficient evidence of festination in both the speech and gait of patients to correctly insist that festination was not a separate entity but rather yet another manifestation of the "shaking palsy".

Parkinson's monograph was favourably received by the medical world. Soon after its appearance, John Cooke, in his *Treatise on Nervous Disease* (1820 - 1823), considered Parkinson's work to "be highly deserving our attention",

and therefore decided to "here give a short account of it, though neurologists have not classed it among the palsies". Although Cooke's 'account' is reasonably full, he ignored completely the speech disturbances. In France, Charcot introduced the eponym "Parkinson's disease", and included the disease in his teaching syllabus. Although from records of Charcot's lectures (see, for example, Charcot, 1887) it appears that he, too, ignored the speech disturbances of Parkinson's disease, McHenry (1969) recently claimed that:

> Charcot would mimick the various gaits, tremors, tics, spasms, cramps and abnormal posture or *voice*[1] of the patients afflicted with the disorder he was discussing. To emphasize a point he would use any means. When he lectured on tremors, he had three or four women brought in who were wearing hats with long feathers, which by their quivering made it possible to distinguish the specific characteristics of tremors in various diseases. It was by such means that he established the differential disgnosis between the tremor in paralysis agitans and disseminated sclerosis.

During the years which followed, Parkinson's monograph continued to influence both the clinical and the research side of neurology. Clinicians concerned themselves with differential diagnoses, and scientists with two aspects - locating the causal lesions, and describing the mechanism of tremor and rigidity. No one, however, considered the speech disturbance, and this, at first glance, is surprising. The years that followed the publication of Parkinson's monograph were years characterized by the efforts to describe the neurological substrates of communication. The work of Bouillard, Max

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[1]writer's own italics

Dax, and Broca provided the impetus for an unprecedented wave of excitement and activity throughout Europe. But, it was to the neurology of language and to the disorders of language - aphasias, apraxia, agraphia, dyslexia, aphonia, amusia, acalculia, and others, that attention was directed. The dysarthrias, and particularly the dysarthria of Parkinson's disease were for the most part passed over.

## THE TRADITIONAL VIEW OF DYSARTHRIA

The consenus of opinion concerning "dysarthria" was that it referred, quite simply, to the articulation produced by weakened muscles. It was easily differentiated from other disorders of communication and its underlying mechanism tacitly assumed to be understood.

Ironically, nowhere is the concept more explicitly stated than in the published proceedings of a meeting held by the Society of Neurology of Paris, held on June 11, 1908. On that day, as on two subsequent occasions, the French neurologists met to discuss aphasia. Provoked, as usual, by Pierre Marie's highly idiosyncratic diagnostic categories and use of the terms "anarthria" and "dysarthria" (co-terminous for Marie, see Marie (1906a), footnote 10 in Marie (1906b) and footnote 9 in Marie (1907) , Dejerine was moved to make the following statement, - and in so doing, provided one of the clearest descriptive definitions of the disorder:

The words *dysarthria*, and *anarthria*, have in semiology a

special meaning admitted by everyone and signifying a difficulty with or an impossibility for the *articulation* of words. The motor asphasic in no way resembles the dysarthric or the anarthric; indeed, when he has conserved the faculty for pronouncing some words, in general always the same ones, these words he generally pronounces very correctly, sometimes emphasizing a little bit as a child does who is learning to talk. But these few words are the *only* ones which he has at his disposal, and he is unable to pronounce *any* other...

How totally different is the condition of the speech in the case of the dysarthric or the true anarthric, whether it be a paralytic dysarthria such as the true or the pseudobulbar, the general paralytic, or the ataxic or spasmodic dysarthric (as in multiple sclerosis). In all these cases only the articulation is affected. Indeed the subject can pronounce *all* words but he pronounces them badly and his language is much more incomprehensible as his dysarthria is more advanced, to a point where - and in the cases with a progressive form (true and pseudobulbars) it is not easy to note - the patient becomes completely anarthric, that is to say, it is impossible for him to articulate any word. And in the case of these subjects - pseudo - and true bulbars - the problems are not limited to articulation of words but include the movements of the lips in the act of whistling and blowing, those of the soft palate - rhinolalia aperta of the voice and disorders of deglutition - difficulty of the tongue - slowness and laziness of movements. They show very well that it is a question here of disorders of paralytic origin, ending eventually in a more or less complete paralysis of these different organs. But one never sees such things in the case of a motor aphasic who has intact the functions of the bucco-pharyngo-laryngeal apparatus for all movements *other* than those of speech.

No one at the meeting challenged Dejerine's presentation of the traditional differentiation between the two disorders. On that, at least, they were all in accord. Marie, for his part, remained equally adamant that he was not concerned with the dysarthria Dejerine defined. "I do not see why, he insisted (1908a), "I should be refused the right to utilize this word to designate problems of articulation in motor aphasia... I have given the name *anarthria* to disorders of articulation which constitute all the symptomatology of the

pathological state today called pure motor aphasia." Later in the same discussion he returned to this point saying: "My contradictors are moved by an erroneous idea,... They suspect me of trying to sustain that my "anarthria" is only a simple disorder of the peripheral organs of articulation. - And in this they are wrong...."

The phrase 'only a simple disorder of the peripheral organs of articulation' succinctly expresses both the scope that the disorder was seen to have, and the dismissive, if not contemptuous, manner with which it was dealt. And indeed, on the surface, there seemed little to be gained (apart from verifying Parkinson's observations), in considering the question in more detail. Disturbed acts of articulation and speaking are speciously simple: if the basic vegetative functions of breathing, of chewing, and of swallowing are disturbed so too will be speech. Parkinson himself observed the co-association of these disturbances. The relationship between these functions is an intimate one, and nowhere is it more beautifully described than in the introductory chapter R.H. Robins wrote in 1971:

> The material of speech, sounds emitted from the vocal tract, is limited, but is range and application, nothing less than the entire furniture of earth and heaven and all our doings therein, is unlimited. Yet speaking is only a by-product, an exploitation of waste: with few exceptions, that do not alter the general picture, speaking is simply the noisy interference with expiratory, used, air as it passes up from the lungs through and over the various organs of speech: glottis, tongue, palate, teeth, lips, nasal passage, etc. Breathing out, expiration, is a biologically essential process of ridding the lungs of air charged with carbon dioxide. The energy expended in additionally interfering with it to make noise, that is, to speak, is minute. In the light of the place taken by language (i.e. by speech) in human life as

we know it, one may challenge anyone to name any other use of spent material that comes anywhere near it in power and significance. Moreover the organs of speech, as they are called, the tongue, the teeth, and so on, are not primarily organs of breathing and the stomach the organ of digestion; they are organs performing a number of functions in the economy of the human body, and speaking, noisily and purposively interfering with spent breath, is just one function superimposed on them.

This view of speech and its dependence on the integrity of innervation is undeniable, but it is not comprehensive enough to explain all the disturbances of speech which occur in Parkinson's disease. Festination, for example, cannot successfully be incorporated into a simple theory of motor dysfunction.

Interest in dysarthria was rekindled in the early part of the twentieth century, and new observations taxed the concept of 'dysarthria' even more. Indeed, observed phenomena were not compatible with the classical theory, and could never have been predicted by it.

## SPEECH DISTURBANCE IN POST-ENCEPHALITIC PARKINSONISM

The encephalitic epidemics that ravaged Europe and Britain during the First World War, left their mark, in a large proportion of patients, in the form of sequelae resembling, in varying degrees, the symptoms of paralysis agitans. Hall (1924) who published an erudite and conprehensive book (based on his Lumleian Lectures delivered before the Royal College of Physicians of London in the preceding year) on the subject of post-encephalitic Parkinsonism, unfortunately makes only the briefest of passing comments on the speech disturbances. All he says

is, "Explosive crying or laughing; repetitions of speech, palilalia (described by Souques in 1908); torsion movements...." European neurologists provide more detailed discussion of speech involvement; at least half a dozen papers were published which treat the topic in some depth.

In the same year that Hall published his book, Leyser provided the first serious clinical description of speech disorders in patients with post-encephalitic Parkinsonism. He defined three types of speech dysfunction: palilalia, an akinetic form and a rigid form. In addition, Leyser made two important observations regarding the speech of these patients. He believed the central characteristic to be one of monotonous, weak speech with vague articulation due to the reduced amplitude of articulatory movements, and *not*, he emphasized, to rigidity, since the facial muscles of these patients are by no means 'rigid'. The second characteristic of their speech, is the acceleration of speech into an unintelligible murmur. Leyser was thus one of the first to accept akinesia as a basis for many of the symptoms presented in the disease. Unfortunately, however, neither the work of Leyser, nor the concept of akinesia introduced by Kinnier Wilson (1925) made much impact on subsequent work. Indeed, the very next year, 1925, saw publication of a paper by Schilling, in which 'rigor' of the vocal folds was suggested as underlying the disturbances of speech.

Schilling's patients (1925) had one characteristic which differentiated them from the series by Leyser: they

all were known to have recently had the disease - from a 'few' months to a 'few' years. Schilling's findings, reported in German, are summarized in English by Grewel (1957):

> The regular undulations of the intermediate rest position of the thorax during vegetative breathing are not seen in these patients. Breathing movements are wider in extent but more irregular than in normal persons. Physiological division of exhalation into a fast and a slow phase is more pronounced than in healthy people, the slow phase being excessively slow. Breathing pauses between the respirations are longer than normal and the relation between thoracic and abdominal respiration is more constant than in normal persons.
>
> During speech the synchronisation of thoracic and abdominal respiration is even more manifest than in quiet breathing. According to Schilling these patients have, during their speech, periods of increasing depth of breathing, alternating with periods of stagnation of respiration. During the periods of propulsivity, when speech changes into a soft murmur, respiration, contrary to articulation, may remain undisturbed, but in other cases, it is shorter and shallower and may even stop. Only rarely paradox movements of the vocal cords are noticed. The range of the voice is considerably decreased, the patients can no longer sing, and in singing, as in speaking, the chest resonance is lost. Speech melody is increasingly monotonous, especially so because the expressive tune (pitch range and shifts of pitch, inflections or glides, and intonation) disappears. Objective speech, eagerness, emphasis, or strong emotions are no longer distinguished. Moreover, rhythm does not change; the patient is monodynamic. Articulation of vowels and consonants is insufficient owing to the impaired movements of lips and mandible. Vowels are pronounced vaguely and "thinly", consonants insufficiently loud and blurred.

In 1940, Cramer published her findings of an experimental investigation of six post-encephalitic patients in the Phonetic Laboratory of the University of Amsterdam. The equipment used included gramaphone recordings of the patients' speech, smoke drum recordings, oscillograms, Wothlo's apparatus to measure exhalation, the head-apparatus of Zwaardemaker, etc. It was a most

thorough study of speech, using the most up-to-date equipment available at the time. Her results are compatible with those of Schilling.

Cramer found respiration to be shallow, with frequent inspirations and a soft or aspirated commencement. Very little difference was found between 'normal' or 'vegetative' breathing, deep respiration, and respiration during reading. In comparison with 'normals', vital capacity was reduced, and inspiration and expiration occurred up to 1½ times as frequently.

The investigations of prosody demonstrated a reduction of pitch range during reading, similarities in 'sentence tune' between parts of the same sentence, between items on a list of bisyllabic words. According to Cramer a reduction in prosodic features, particularly the downward inflection at the end of phrases or sentences was found to be lacking. Concerning singing ability, Cramer considered that provided due allowance for the disturbances of respiration and articulation were made, patients were able to sing a well-known tune 'reasonably well'. Stress patterns were generally undisturbed (although some deviations were observed), while timbre was found to be altered.

Articulation was so disturbed as to reduce speech, in some cases, to a 'murmur'. Syllables, it was found, might be repeated, omitted, and superflous ones added. Phonemic identification was often impossible in the speech of patients, but when they were identified, it was observed that certain phonemic changes occurred,

such as explosives being substituted by fricatives (e.g. imperfect /s/ and /z/ for /t/ and /d/). Cramer believed this to be a direct consequence of the rigid state of the articulatory muscles, and demonstrated this using two sets of apparatus. The head-apparatus of Zwaardemaker produces a graph representing the movements either of the mouth or the lips. In 'normals', the graph is characterized by variations of fluctuations that corresponded to vowels and consonants in speech. These flunctuations are characteristic and easily identifiable. In the post-encephalitic Parkinsonian patients, the graphs were so flat as to be virtually a straight line. The 'width of mouth opening' graph was found to be so little differentiated that the distinction between vowels and consonants was extremely difficult, and the identification of the different vowels impossible. A similar picture was found in the curve depicting lip movements. The normal excursions of the graph for articulation sounds is much reduced in those patients, and all that is seen are slight waves in the graph, which cannot be, with confidence, differentiated from a graphic representation of tremor in the muscles concerned. The second apparatus, a smoked drum, also provided graphic representation of movements. For this investigation, patients were required to make sounds (e.g. 'zaa' or 'aas') or imitate movements (e.g. yawn or grind their teeth) which necessitated large movements of the mandible. Only a negligible range of movement was demonstrated. Whether in fact this indicates, as was supposed, that rigidity

underlines the articulatory disturbances manifest by the patients, is open to challenge. It is far more plausible to postulate akinesia as the basis for reduced range of movements than the rigidity adduced by Cramer.

Rate of utterance was found to be slow. This, Cramer observed, to be due to the length of both pauses and syllables. When smoked drum recordings were made of patients' readings, the post-encephalitic Parkinsonian patients were shown to speak less words per unit time, and to have more pauses than 'normals'. Furthermore, when patients read the passage, it was found that their 'syllabic length' was 1½ times greater than that of 'normals', but, interestingly, patients read a series of unconnected words faster than the normals.

Grewel (1957) confirmed many findings made by previous workers, and also added new observations to the growing collection of data. He agreed with Cramer and Schilling in their descriptions of breathing, phonation, and articulatory disturbances. He confirmed their findings regarding the narrowing of pitch range, restriction of stress and intonational patterns, and on the one point where Schilling and Cramer differ, he supported Schilling and maintained that post-encephalitic Parkinsonian patients are unable to sing.

In addition, he observed that after the onset of acute encephalitis, speech is slow and difficult. He noticed "hyperkinetic phenomena: clonic stuttering, logoclonic repetitions at the beginning or at the end of a word, hyperkinesia of the tongue and the mandible

and accelerated speaking". And in a small number of cases there were more profound disturbances. These he listed as "conspicuous interruptions of the speaking drive, palilalia, and/or impulsive shrieking-, wailing-, and howling-attacks".

He agreed with Schilling in his observation of festination ending in dysphonic, or even in some cases, aphonic murmurings. But he went one step further, and saw in the phenomenon 'compulsive' aspects: "In rare cases this murmur continues 'automatically' for some time, the patient being apparently unable to interrupt this stream of abortive speech."

However, Grewel's most important contribution must be this observation: "The patient has a growing difficulty with the start of speech; a certain hesitation, a slightly tonic drawing or trailing noticed at the start, and finally it is manifestly difficult to initiate speaking movements at all, as in the case with any other movements in post-encephalitic Parkinsonism." It is indeed a somewhat contradictory, and most interesting, picture of the speech of these patients which emerges from the literature. On the one hand there is difficulty in starting speech which Grewel described so well, and on the other, difficulty in stopping, noticed by Schilling and confirmed by Grewel. Unfortunately, Grewel comments neither upon this picture nor how it can be subsumed under the rubric of dysarthric disturbance.

Grewel identified four factors as being responsible for the dysarthria: the 'impaired achievement of

intended innervations'; festination (his 'phenomenon of propulsivity'); rigidity and hypokinesis; and pseudo-dysdiadokokinesis. 'Pseudo-dysdiadokokinesis' is an impairment of the subtle co-ordination of muscles, and according to Grewel is possibly the most important factor of all.

## A REVIEW OF LITERATURE FROM CIRCA 1950

The publication by Trétiakoff (1919) of observed cell loss in the pars compacta of the substantia nigra in the brain of Parkinsonian patients led to a reassessment of the pathogenesis of the disease. More recently, in the late 1950's in particular, several developments in the theory and method of treatment of the disease were reported. The possibility of being able in some way to mitigate the invariable progression of the disease, and the prospect of being able to take the first steps towards an understanding of the mechanisms underlying both symptoms and disease process, enabled the patient and his disabilities to be seen in a new light.

This change in climate affected also those disciplines which considered communication and its disorders within their sphere of study. After 1950, an increasing number of speech pathologists, audiologists, psychologists, psychophysiologists and psychoneurologists investigated the function and 'dysfunction' of the basal

ganglia, and the reports of these investigations were no longer published solely in neurological journals. This multidisciplinary approach lead to investigations on a broad scale. To a problem indeterminate in concept, classification and terminology, the behavioural scientists brought new methods, new tools, and new theories. While the quality of the experimentation arising from this collaboration is often disappointing, the collaboration itself has been most productive. In comparison to the paucity of research prior to the 1950's, the later period is characterised by both the wealth and the breadth of its research.

There is no comprehensive review of this work; Calne (1970) in his recent monograph devotes only one paragraph to speech. This section is an attempt to fill the gap: it is concerned primarily with the question of speech disturbance associated with lesions of the basal ganglia, but it shall, if in only a cursory manner, draw attention to the scope of work as a whole that arose from the interdisciplinary collaboration.

The modern work on speech falls into two categories. There are studies which in essence are attempts at scientific or objective corroboration of the descriptive writings based on clinical observation. If any general conclusion is to be drawn from this work it must be that a trained ear is a reliable assessor of speech disturbances, and in many ways superior to equipment available at present. The second group of studies are characterized by an approach which satisfies at least one requirement of

scientific experimentation. Based as they were upon observations of behavioural changes during or after stereotactic surgery for the relief of Parkinsonism, they have as the identifiable and measurable independent variable the electrical stimulation and/or an induced lesion. However, reports similar to Marion Smith's (1967) suggest that the location of surgical lesions is imprecise and question both the validity and the reliability of the method. Differences in surgical techniques used by different neurosurgeons make assessment of reliability difficult. Furthermore, although a new range of experimental possibilities is offered by this method on a practical level, investigations are restricted by ethical considerations.

## DESCRIPTIVE STUDIES

In the early 1960's, Gerald Canter, a speech pathologist, investigated a group of seventeen Parkinsonian patients. His work is fully documented in his PhD dissertation (1961), and a series of three articles based on this work (1963, 1965a, and 1965b). The work itself falls naturally into two parts. The first is essentially an objective (or, as Canter described it a "scientific") description of the patients compared to an age-matched control group. In many ways this part of Canter's work closely parallels that of Cramer's carried out twenty years earlier. For all the sophisticated apparatus and laboratory expertise at his disposal, for all his care in

establishing reliability of equipment before embarking upon the study proper, for all the number of parameters investigated, and for all the time spent on many of the analyses (e.g. pitch analysis of each subject's test-sentence took between one and two hours), Canter's work on the whole is disappointing. Data so meticulously collected and analysed warrants statistical treatment in a manner more sophisticated than the mere recording of means, medians and ranges for the 'experimental' and 'control' groups on all parameters. Nevertheless, reported within this first part of Canter's work are three extremely interesting findings.

Canter looked at a number of parameters which define what he terms "physiological support" for speech. These were chosen because they measured maximum performance levels of the speech mechanism, and on all parameters patients performed far less well than the controls. Patients were found to have reduced pitch and loudness ranges; to be unable to produce sounds as high- and as low-pitched, or as loud and as soft as the controls; to be unable to sustain phonation for as long as the controls could; and, to have lower diadokokinesis rates than the controls. Canter believes his findings indicate that patients do not utilise their "maximum function for speech", and that the basis of this is not a reduction of "motivation for effective communication" (as Zimmerman et al., 1959, for example, believed), but rather, a reduction of the "physiological support" necessary for adequate speech. Canter believed that to improve speech in these

patients efforts should be directed towards extending the physiological support rather than towards increasing "motivation".

His reasoning is most persuasive. He states that:

> ... many of the patients were already employing a large proportion of what would normally be 'reserve function' for simple continuous speech. In addition, their reserves were so limited that even if they had employed their maximum capacities for continuous speaking, speech would have remained defective. Moreover, clinical experience suggests that when an individual has to operate close to his maximum for conversational speech, or to 'dip deeply into his reserve', the fine control necessary for efficient speech production is impaired even further.

On the physical parameters that correlate with what is perceived as 'loudness', Canter found that the patients did not appear to perform in a markedly different manner from the controls. This finding that patients spoke as loudly as controls is neither what Canter himself expected, nor what one is led to believe from the literature. Canter suggests as plausible explanation that the perceived loudness reduction is in fact listener-error. As Canter summarises it: "It was speculated that the impression of inadequate loudness in the speech of some of the Parkinsonian patients might have been due to the added perceptual effort demanded of the listener in his attempt to understand these patients' indistinct articulation." There is, however, another factor that Canter does not account for. Canter's patients were all ambulatory, and hence, were not markedly impaired in general motor activity, nor, presumably, in speech function. It may well be that listener-judgement of reduced loudness has physical correlates measurable on current methods only in

later stages of the disease. Production of sound for speech is a gross motor act, requiring little of the fine co-ordination other aspects of speech, such as articulation, demand. It seems reasonable to expect that as the severity of the disease progresses, mean sound-pressure levels of patients would gradually differentiate themselves from those of controls. No one to date has attempted such a longitudinal study, although the results would be interesting. Intuitively, the corollary would seem plausible. If one were able to reverse the progression of the disease in a patient whose voice was shown clearly to be reduced in loudness, one would expect voice volume to increase before improvements in articulation, etc., were apparent.

Canter found another puzzling phenomenon. When comparing the way his patients and controls performed on the variety of test parameters, he found that the patients tended to differ from each other as much as they differed from the controls. This failure to demonstrate a consistent profile of the characteristics of Parkinsonian speech is unexpected. It could be a product of Canter's sampling procedure; or it may be that a trained ear is superior to present technology for the identification of distinctive patterns of disordered speech. For distinctive and identifiable they indeed are. Darley et al. (1969a, 1969b) have clearly demonstrated that their panel of three judges were able to identify ten dimensions which successfully differentiate the speech of Parkinsonian patients from the speech of patients with

other neurological involvement. This cluster of dimensions which was empirically demonstrated to have predictive value closely resembles the collective observations of previous workers:

> The 32 patients in the parkinsonian group presented phenomena constituting what may be called "hypokinetic dysarthria".... All four of the neurologic groups[1] previously reviewed displayed *monopitch*[2] and *monoloudness*, but the severity of these dimensions is decidedly greater in parkinsonism; together with *reduced stress* they comprise the most striking phenomena. Related prosodic changes distinctively present here are *inappropriate silences*, *short rushes of speech*, and *variable rate*. It will be seen that this is the only type of dysarthria in which rate is not characteristically slow; it is typically quite variable and, considering the group as a whole, is rated as slightly fast rather than on the slow side. *Imprecise consonants* is prominent, apparently being the result of reduced excursion of the articulators rather than simply the rate of articulation. Both *harsh voice* and *breathy voice* are heard.

The second part of Canter's work marks a significant change in the design of investigations. Previous work on speech disturbances (with the notable exceptions of Cramer's, and of course, Canter's own laboratory studies) was based on clinical observation of patients. Canter was the first to set up a situation in which a panel of sophisticated listeners were required to make judgements about pre-recorded samples of Parkinsonian speech. Canter asked three judges to rate the recordings (from 'best', Rank 1, to 'worst', Rank 17) on two parameters: clarity of articulation, and overall speech adequacy. On the basis of these two sets of ratings together with several

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[1] bulbar palsy, pseudobulbar palsy, amyotrophic lateral sclerosis, and cerebellar disorders

[2] names of 'dimensions' are in italics

parameters of disease history and symptomatology, a series of correlations were carried out. It was shown that clarity of articulation correlated highly with judgements of adequacy of speech, that longer duration of illness and that disease of post-encephalitic origin tend to be associated with inadequate speech. However, Canter was unable to demonstrate any relationship between adequacy of speech and degree of tremor or rigidity.

Canter's final correlation represents a theoretical watershed. He adduced the possibility that dysarthria might depend on higher, or more central, neural functions. Canter introduced the topic thus:

> The importance of the left cerebral cortex in speech and language functioning is well recognized. Little is known concerning subcortical localization of function, however. It was speculated that patients whose motor impairment was predominantly on the right side of the body, and who could therefore be presumed to have greater involvement of the left side of the brain, might have more severely defective speech than the patients whose symptoms were predominantly on the left side of the body, and whose neural involvement was presumably greater on the right side of the brain.

The second half of this century has been characterized by a pre-occupation with asymmetry of functional representation in the brain. At least one major neuropsychological conference has taken place dealing exclusively with this topic (see Mountcastle, 1962). It is not surprising that the question 'Does laterality of brain-damage have an effect on speech (as opposed to language)?' be asked at this particular point in time. Approached from the other side, however, the question is indeed extraordinary.

Dysarthria has persistently been defined in a manner most restrictive and fully consistent with the traditional concept outlined in a preceding section of this chapter: it was a 'disturbance of articulation' and no more. Peacher, over two decades ago, pointed out the need to up-date the formal definition to include more than articulation. He believed current usage of the term indicated an extension of the concept to include, in addition to articulatory disturbance, disturbances of resonance, of stress patterns, etc. (Peacher, 1950). Grewel (1956) went further and made out a most persuasive case for using the term in the *plural* form by illustrating that the 'dysarthrias' in the various neurological categories are sufficiently different and identifiable to warrant this. However, neither Peacher and Grewel, nor indeed any of the speech pathologists or neurologists who held similar views, went any further than pressing for a redefinition along more empirical and practical lines. No-one challenged the basic constraint of the concept, i.e. it was a disorder of motor, effector or peripheral function due to paralysis or paresis of muscle. In fact Darley et al. (1969a) are explicit on both the scope and limits of the definition of dysarthria they subscribe to. In an article, *Patterns of Dysarthria*, they explain that they:

> ...will use the traditional term "dysarthria" but will use it to encompass coexisting motor disorders of respiration, phonation, articulation, resonance, and prosody (those variations in time, pitch, and loudness which summate to produce emphasis and interest in speech). However, the term will be restricted - again in accordance with modern usage - to speech dysfunctions that are neurogenic.

The concept of dysarthria emphasised the symptoms and ignored completely aspects such as the site of the lesion and the mechanism of symptom production. Even with the amendments for which Peacher and Grewel pressed, 'dysarthria' remained a somewhat sterile concept - a label.

Canter's findings regarding laterality and speech are disappointing. His data gave no indication that the patients with predominantly right-sided symptoms and those with left-sided symptoms were "systematically different in speech adequacy". Instead, his findings regarding patients with bilateral involvement support both Parkinson and the traditional concept: his three patients with bilateral affection had relatively inadequate speech. However, the question which Canter asked is one which will be found with increasing frequency in subsequent research, for new techniques of neurosurgery were introduced that lent themselves particularly well to the investigation of laterality and speech.

## THEORETICAL CONSIDERATIONS

> Traditionally all intellectual functions including speech and language have been thought to be located in the cerebral cortex, and more speculations have been directed to this thin sheet of tissue than toward any other cerebral component. However, there are many other structures that are demonstratably connected with the cortex and with each other (often only by circuitous routes). Every structure of the brain is physiologically active and at least some of the structures have been

> hypothesized to play a part in the same intellectual functions that are more frequently imputed to the cortex.
> *Lenneberg, 1967.*

At the beginning of the century, in 1906, Pierre Marie "startled the medical world" (Head, 1926) with three papers in Semaine Médicale on 'Revision of the Question of Aphasia' (Marie, 1906a, b, c). In this aggressive manner, Marie began a dialogue, at times extremely heated, with the champion of the orthodox doctrines of aphasia, Dejerine. Marie's theories are extremely interesting: it is his concept of 'anarthria' that is particularly germane here - the interested reader is referred to Marie's own writings and to Head (1926) for full treatment of the theories pertaining to aphasia. Suffice it to say here, concerning Marie's concept of aphasia, that "...according to Marie, there is only one true or primary aphasia, that of Wernicke, characterized by some loss of intellectual aptitude. When to this is added 'anarthria', we have the syndrome known as 'Broca's aphasia'." (Head, 1926).

According to Marie, verbal communication consists of two aspects - "interior" speech and "exterior" or "articulated" speech. His distinction is virtually identical to that advocated by de Saussure in his Cours de Linguistique Générale (1916), the distinction between "langue" and "parole" which so influenced modern linguistics. For Marie (1908a) a disturbance of "interior" or "articulated" speech manifests as *aphasia*, and a disturbance of "exterior" or "articulated" speech as

*anarthria*. Anarthria does not refer merely to disturbed articulation of sounds or words; it is a comprehensive concept including a wide range of disorders from phonation (Marie, 1908b) through intonation (Marie, 1906a) to rate of speech (Marie, 1917). Of particular interest is Marie's localization of this sensorimotor aspect of communication. On the basis of clinical experience and post-mortem evidence Marie believed that sub-cortical structures were involved: "For *anarthria*, ...the lesion is [in] the region of the lenticular nucleus, either in the nucleus itself, or in the anterior part and the knee of the internal capsule, or in the exterior capsule." (Marie, 1906a). Marie thus describes a "quadilateral zone of anarthria" in a horizontal plane; he was not able to delineate the superior and inferior limits of his 'quadrilateral' (1906d, 1907).

It is interesting that although Marie recognized that the right hemisphere played an equal part with the left in the production of anarthria (1906a), he did not elucidate why this might be so. However, he did point out that anarthria arising from bilateral lesions in the zones of the lenticular nuclei is more pronounced and tended to be permanent (1906b); anarthria arising from unilateral lesion/lesions tended to be transient and less pronounced.

It is surprising, and not a little disappointing that Marie did not extend his theory of anarthria to include palilalia. Having written: "In cases where anarthria is due to a lesion of the lenticular nuclei in the two

hemispheres it can remain persistent, and then it often coincides with the syndromes of pseudobulbar paralysis" (1906a), it appears to be a small step to include palilalia, a disorder first seen only in pseudobulbar palsy, within the scope of his theory. Perhaps Marie shelved the question of palilalia too long; in 1925 when his second and last paper on palilalia appeared, (three years after the first), Pierre Marie retired.

The second major theory concerning the role of subcortical structures in communication was proposed by Penfield, based largely on cortical electro-stimulation studies, carried out together with Roberts. The problem as Penfield and Roberts saw it is explained in this extract (1959):

> It has long been assumed that the cerebral cortex was the summit, funtionally speaking, and that the business of the mind was somehow transacted there. The transactions were somehow to be carried out there by means of "association" areas of cortex and the transcortical fiber systems. According to this conception, the visual information that came from the right half of the visual field to the left hemisphere would have to be made available across the hemisphere to the precentral gyrus, so that appropriately patterned impulses could be sent out to the right hand. But what about the other hand, and the other field of vision, and what about the plan of action?
>
> It is obvious that the brain must have a central coordinating and integrating mechanism. If this "machine" is at all like other machines, there must be a place towards which streams of sensory impulses converge. There must be a place from which streams of motor impulses emerge to move the two hands in simultaneous, planned action. There must be neuronal circuits in which activity of both hemispheres is somehow summarized and fused - circuits the activation of which makes conscious planning possible.

In 1936, Penfield argued the case for locating this "integrating system" within the diencephalon. He believed there to be "evidence of a level of integration

within the central nervous system that is higher than that to be found in the cerebral cortex." Furthermore, he believed there to be a "regional localization" of the neuronal mechanism involved in this integration which is

> most intimately associated with the initiation of voluntary activity and with the sensory summation prerequisite to it.... All regions of the brain may well be invovled in normal conscious processes, but the indispensible substratum of consciousness lies outside the cerebral cortex, ... not in the new brain but in the old... probably in the diencephalon.

By 1952 Penfield had a name for his system - the "centrencephalic system", a term he preferred to "highest level of integration" suggested by Jackson; Penfield disliked the connotation of Jackson's term, i.e. of a separation between functional levels, and he disagreed with Jackson's implication of the frontal lobes in integration. And by 1959, Penfield had enlarged his system

> to include "the integration of varied specific functions from different parts of one hemisphere".... The subcortical coordinating centers... for speech are integrating areas within one hemisphere. Thus, although the centrencephalic system would not include the cranial nerve nuclei of the brain stem, it would include all those areas of subcortical gray matter (together with their connecting tracts) which serve the purposes of inter-hemispheral integration and intra-hemispheral integration.

More specifically, on the basis of three sources of evidence - on extrapolation from research on monkeys and apes; from his own electro-stimulation of the human cortex; and from clinical studies - Penfield proposed the following mechanism: the "posterior speech area", i.e. Wernicke's, is reciprocally connected to the pulvinar and

nucleus lateralis - posterior of thalamus; the supra-marginal gyrus, i.e. the supplementary motor area, to the pulvinar; and the "anterior speech area", i.e. Broca's, to the centrum medianum. While accepting that transcortical association tracts "are of importance, no doubt", Penfield maintained that they are "certainly of less essential importance than *subcortical integration*". Penfield envisaged a "functional relationship" between cortical areas via thalamic projections ("it is proposed, as a speech hypothesis, that the functions of all three cortical speech areas in man are coordinated by projections of each part of the thalamus, and that by means of these circuits the elaboration of speech is somehow carried out."). Furthermore, Penfield viewed 'speech', as opposed to 'language', as being bilaterally represented ("There are no areas for ideational mechanisms of speech on the non-dominant side, although the motor mechanisms are the same as on the dominant side."). He offered in support of his view, the observation that stimulation of either the dominant or non-dominant "voice control area" (in the lower portion of the precentral gyri) produces vocalization, and that a lesion in either the dominant or non-dominant "voice control area" produces "dysarthria".

The theories of Marie and Penfield, while concerned with essentially similar areas of the brain, are diametrically opposed. Marie sought to identify and to distinguish between the neurological substrates of language and of speech; Penfield sought to describe the

substrate of all higher mental functions from speaking to thinking, reading and writing. There are, however, two aspects common to both theories: they both are based on inference, and they both stress the importance of subcortical structures in verbal activity. Marie ascribed the function of the motor elaboration of speech to the subcortex; Penfield ascribed the function of mediating between cortical areas. An interesting and critical question follows: if one were able to place discrete lesions in specific parts of the subcortex of man, what *would* result?

## STEREOTACTIC SURGERY AND ITS EFFECTS ON COMMUNICATION

A common means of treatment for rigidity and tremor in Parkinsonism is the stereotactic induction of a lesion, usually in the ventrolateral nucleus of the thalamus or pallidum. The most consistent result that emerges from the numerous reports of these stereotactic procedures is congruent with the theoretical predictions made by both Marie and Penfield: communication skills are closely related to the functioning of subcortical structures. While thalamotomy and pallidotomy undoubtedly reduce tremor and/or rigidity, they frequently have the unfortunate side-effects of exacerbating, and in some cases of inducing, speech and language deficits. Cooper (1961), for example, found that in about 10% of patients who had undergone unilateral surgery, speech deficits were manifest in the first two post-operative weeks.

Bilateral surgery appeared to have an even more drastic effect: out of 100 consecutive patients who had undergone bilateral intervention, 18 experienced speech disturbances, and 6 were left with "a lasting handicap, which simulated the speech of pseudobulbar palsy". Similar results have been reported by Waltz et al. (1966), Hermann et al. (1966), and Spiegel et al. (1965). In 1969, Hankinson stated that "the most persistent, troublesome, and widely reported complication of bilateral thalamic lesions for Parkinsonism is speech disturbances."

The first question to ask is: Are the induced deficiencies in communication due not to the stereotactic lesion placed in the subcortex, but, rather, to the passage of a surgical instrument through the cerebral areas on its way to the subcortical target?

Riklan and Levita (unpublished data reported in Riklan and Levita, 1969) appeared to be the only ones to have observed Parkinsonian patients during surgery with this question in mind. Using brief tests of language function "with an emphasis on alertness, orientation, vocabulary, conversation, recent recall, mental control, and the naming of common objects", they established that

> ... the passage of the chemo- or cryosurgical cannula through the cortex, the underlying white matter, and up to the sub-cortical target area, was not associated with any observable language or cognitive disturbance, regardless of laterality of subsequent lesion placement ... In contrast, on occasions, apparent alterations in linguistic fluency were associated with the passage of the cannula through the thalamus or with the cooling of the thalamic target following appropriate placement of the cannula... Moreover, encephalographic studies before

and after cryosurgery lesions of the thalamus... suggest that widespread edema is not a likely secondary physiological consequence of surgery.

This finding is closely related to, and supported by Bell's (1968) more general observation that "neurological disorder may follow the making of a burr hole, but that there is no recorded evidence that such a procedure has resulted in dysphasia".

Three major types of communication disturbance are consequent upon the stereotactic placement of subcortical lesions: diminished voice volume; dysarthria; and dysphasia.

Diminished Voice Volume

Allan et al. (1966), Hermann et al. (1966), and Bell (1968) have reported that stereotactically induced lesions lead to a diminution of pre-operative voice volume levels. Hermann et al. (1966) found that unilateral left lesions were more frequently followed by voice volume reduction: 67% of patients undergoing left-sided surgery exhibited this reduction post-operatively as compared with 56% of patients who had undergone bilateral or multiple surgery, and 36% of patients who had had right-sided surgery. Furthermore, they report that the lesion causing this reduction of voice volume involved the internal capsule. Bell (1968) however, established a clear relationship between bilateral surgery directed towards the ventrolateral nucleus of the thalamus, and post-operatively diminished voice volume. In addition he found that this diminution was relatively transient, and improved in the

immediate post-operative period. In the case of a dominant hemisphere lesion, however, the disorder residual after three weeks tended to persist, whereas following a lesion in the nondominant hemisphere in some cases voice volume continued to improve for "some months".

Dysarthria

Speech disorders are a common sequel to subcortical surgery. Hermann et al. (1966) and Allan et al. (1966) (reporting on the same group of 118 Parkinsonian patients) suggest that the pre-operative Parkinsonian speech disturbances are exacerbated by subcortical surgery, and in particular, by unilateral left surgery involving the internal capsule. Bell (1968), however, demonstrated that the dysarthria exhibited following thalamotomy is a product of surgery and independent of the pre-operative Parkinsonian speech difficulties:

> The pre-operative speech disorder appeared to be exaggerated in only a few cases. The nasal intonation of the voice of one patient was accentuated and two had an increase in a difficulty in starting to speak. In five cases [out of a total of 59] the diminished voice volume and slurring present before operation were accentuated. In other cases with a pre-operative slurring of speech, the post-operative dysarthria was qualitatively different, being accompanied by a marked change in the pitch of the voice. Fourteen patients with a post-operative speech disorder had not had a detectable pre-operative speech disorder. The suggestion of a relationship between the speech disorder after thalamotomy and the pre-operative Parkinsonian speech disorder was not confirmed on statistical analysis.

That speech difficulties are frequently consequent upon subcortical intervention is particularly significant. In itself this observation supports two hypotheses: one that damage to subcortical areas interferes with speech,

and, secondly, that rigidity and tremor, which are improved by surgery, are not related to speech since this is far from improved by surgery. This latter hypothesis is well supported by Canter's findings (1961), that severity of dysarthria in (unoperated) Parkinsonians is not related to degree of rigidity or tremor.

What mechanism, then, underlies both the pre- and post-operative dysarthria? Leyser (1924) suggested akinesia as a possibility, and the evidence, meagre as it is, seems to bear this out. Since stereotactic surgery is effective in reducing tremor and rigidity, but has no beneficial effect on akinesia (Bell, 1968) it is to be expected that the bias in selection of patients is towards those with positive symptoms (i.e. tremor and rigidity). That this group of patients after surgery do in fact exhibit a disturbance of motor function qualitatively different from either rigidity or tremor has been demonstrated by Krayenbühl et al. (1965). They found that "locomotor impulses" were not always continuous nor were they automatically integrated and coordinated following dominant hemisphere intervention.

This finding, together with observations of qualitative differences between Parkinsonian dysarthria and induced dysarthria in Parkinsonian patients who have undergone surgery, is particularly significant. In post-operative dysarthria Bell observed increased difficulty in the initiation of speech. Riklan and Levita (1969) observed similar qualitative differences:

twenty per cent of their patients after surgery exhibited "hesitations or dysfluencies in all aspects of overt verbal expression". All three observations - Krayenbühl's of disturbed motor function, Bell's of initiation difficulties and Riklan and Levita's of dysfluencies - are perfectly compatible with the conclusion that stereotactic surgery exacerbates and/or induces akinesia, and that speech disorders in Parkinsonism are manifestations of this underlying akinesia.

Riklan and Levita's (1969) and Bell's (1968) observation of post-operatively altered tempo of speech relates well to reports of observation of the effect of stimulation of subcortical structures during surgical intervention. Electrical stimulation of deep structures in the brain has one particularly striking effect on speech; it alters the rate of utterance. During stimulation of the ventrolateral nucleus of the thalamus near its junction with the internal capsule, Guiot et al. (1961) observed that the rate with which the patients count was either accelerated or slowed down to the point of total arrest. This phenomenon according to Guiot et al. "appears to be conscious and the patients are subsequently critical of it". Van Buren (1963), however, obtained different results: it was from stimulation of the head of the caudate nucleus or from the adjacent white matter of the frontal lobe and/or the frontal limb of the internal capsule but *never* from within the thalamus that he was able to produce speech acceleration or arrest. Furthermore, in Van Buren's investigation "the patient

never mentioned them [the speech arrests] spontaneously and indeed often seemed to be totally unaware that anything out of the ordinary had occurred". An interesting finding by both Guiot et al. and Van Buren is that arrest or acceleration of speech appears at a lower stimulation threshold than that for arrest of movement.

Neither of these papers appears to have taken hemisphere dominance into account. Hassler (1966) who obtained similar speech results from stimulation of the ventrolateral thalamus also ignored the question. Parigi et al. (1964) simply reported contralateral sensations of noise and an "inability for spontaneous language and compulsive emission of two words following stimulation of the ventrolateral thalamic nucleus in a Parkinsonian patient" without reference to laterality of stimulation. Schaltenbrand (1956) who found that stimulation of VL produced primitive vocalization (much akin to the type of primitive speech Penfield produced by stimulation) also did not report whether there was a difference between left or right hemisphere stimulation. Krayenbühl et al. (1965), however, added a footnote to the Guiot et al. (1961) results: "the motor modification of speech, which consisted in inhibition, slackening or acceleration" were *never* obtained on the "non-dominant" side.

Dysphasia

The side effect of dysphasia following stereotatic surgery directed at the ventrolateral nucleus of the thalamus in particular is, as Bell (1968) phrases it,

"compelling evidence for the participation of the thalamus of the dominant hemisphere in the formulation of speech". Unfortunately, the literature on this topic is often unsatisfactory, and despite Bell's enthusiasm, several issues remain unsettled.

Dysphasia is a frequently referred to side-effect. Mundinger and Riechert (1963) reported dysphasia in all but 5 of a series of 18 cases; Allan et al. (1966) and Hermann et al. (1966) reported dysphasia in 9 out of 118 patients; and Bell (1968) in 9 out of 53. It has also been described by Cooper (1961), Laitinen (1966), Lin and Cooper (1960), Selby (1967), Spiegel and Wycis (1962), Waltz et al. (1966) and Watkins and Oppenheimer (1962). There are, however, reports (such as that by Markham and Rand, 1963) which positively exclude dysphasia as a side-effect, and reports (such as that by Bravo et al., 1966) which, although dealing with speech disturbances consequent upon subcortical stereotactic surgery, ignore the possibility of dysphasia.

Most papers have disregarded the question of hemisphere dominance. Markham and Rand (1963) and Bravo et al. (1966) stated neither the lateralization of the lesion nor the handedness of the patients. In a discussion of bilateral thalamotomy, Gillingham et al. (1964) did not mention handedness, although the occurrence of dysphasia after lesions of the dominant hemisphere in unilateral thalamotomy had been noted in an earlier paper (Gillingham et al., 1960); these findings were confirmed in Hermann et al. (1966) and Allan et al.

(1966) in which 3 of 118 patients were left handed, and 2 of these 3 exhibited post-operative dysphasia.

Of the reports that did take hemisphere dominance into account, some found that dysphasia after thalamotomy were more frequent with lesions in the dominant hemisphere (Allan et al., 1966; Bell, 1968; Cooper, 1960; Selby, 1967; Hermann et al., 1966; Riechert, 1964) 1964), but others denied a correlation (Krayenbühl et al., 1961; Waltz et al., 1966). Dysphasia has also been reported following dominant hemisphere pallidotomy and palliansotomy (Cooper, 1956; Gillingham et al., 1960; Mundinger and Riechert, 1963; Spiegel and Wycis, 1962; Svennilson et al., 1960). Hermann et al. (1966) found that dysphasia never resulted from pure capsular lesions.

Bell (1968) has characterised the nature of the language deficit induced by surgery particularly well:

> The dysphasia varied in severity from a mild difficulty in finding words and in naming objects to a disorder which rendered the patient's speech almost incomprehensible... Verbal output was reduced, there were disturbances of rhythm and modulation of speech even in the two cases without accompanying dysarthria, and all patients, including those unable to emit a meaningful sentence or proposition, had relatively preserved comprehension of speech. Repetition was normal. Rapid fatiguability was prominent in the more severe disorders... In the mild cases the speech was laconic and hesitant with periods of silence while the patient groped for words. In all of the mild cases the patient claimed he knew what he wanted to say. The least affected patient was unable to name such objects as a ball-point pen and the cord of a venetian blind. Some patients misnamed objects occasionally, and one patient in this group had some impairment of grammar.... In only one of the mild cases of dysphasia did the patient have some impairment of consciousness.
>
> The dysphasia of moderate severity was similar, but in addition the speech was sometimes not comprehensible because of difficulty in word finding, and the use of paraphasias and faulty grammar.

In cases of severe dysphasia, there were additional difficulties. Words were "garbled" and found with extreme difficulty. One patient, for example, six days post-operatively, "misnamed objects, and was unable to name the year spontaneously, but she was able to select it and repeat it after hearing it spoken in a series of names and dates". Another patient with extreme naming difficulty, in his groping for words produced disjointed explanatory phrases; for example six days post-operatively he referred to his operation as "cutting skull". He went on to say: "Weekend of medicine... closed for a week pretty well... X-ray ... local after a while. They charge it twelve times". Patients also exhibited reading difficulties, and perseveration. Although this group of patients did have some impairment of consciousness, Bell felt it was possible to distinguish their speech problems from the paraphasic misnamings described by Weinstein and Kahn and from "non-aphasic" misnaming by Geschwind.

The presence post-operatively of perseveration is interesting. One of Bell's patients perseverated in both "spoken and written speech" for "months" after his operation. Allan et al. (1966) also observed perseveration but as a more common post-operative feature in their dysphasic patients. Allison and Hurwitz (1967) demonstrated that the perseveration in dysphasia due to thalamotomy is similar to the perseveration in dysphasia due to cortical lesions. This supports Allison's earlier contention (1966) that perseveration in dysphasia following cortical lesions indicated a disturbance of the

speech mechanism at the subcortical level.

For Bell, this picture of difficulty in word naming, reduced verbal output, disturbed syntax and the inability to emit a meaningful sentence and proposition in the presence of relatively preserved comprehension of speech is characteristic of *expressive* dysphasia. Several other authors who have observed post-operative dysphasia concur with this. Watkins and Oppenheimer (1962) described "a definitive nominal dysphasia but no receptive defect". Selby (1967) found slight expressive difficulties in the presence of unimpaired comprehension in 42.1 per cent of 126 unilateral thalamotomies of the dominant hemisphere. Riechert (1964) referred to "speech disturbances of the motor aphasia type, or of subcortical aphasia type", and Mundinger and Riechert (1963) noted a word-finding disorder. Hermann et al. (1966) and Allan et al. (1966), however, came to the opposite conclusion - that it was a *receptive* disorder - although their brief description (see Allan et al., 1966) nevertheless is of a disorder indistinguishable from that described by Bell and the above-mentioned authors.

It is difficult to evaluate reports of general intellectual deficits and impaired psycholinguistic and psychomotor abilities following subcortical surgery. Riklan and Levita (1969) suggest: "The presence of conflicting findings in the literature may be attributed, partly, to frequent omission of operational definitions, to the absence of adequate control procedures, and to a lack of objective and quantifiable data". For example,

of 8 investigations pertinent to the question of the psychological effects of unilateral surgical intervention, only 3 (McFie, 1960; Riklan et al., 1960; Krayenbühl et al., 1965) were based on statistical analysis of standardised test data. Although quantifiable indices were collected in another study (Fuenfgeld, 1961) the conclusions were not derived from statistical analysis. The 4 remaining studies (Bonduelle and Guillard, 1962; Gillingham, 1960-61; Krayenbühl and Yasargil, 1961; Mueller and Yasargil, 1959) are essentially summaries of subjective evaluations and impressionistic findings. None of these studies made adequate use of control groups. Pre- and immediate post-operative intervals between evaluations varied widely, and in two studies (Gillingham, 1960-61; Krayenbühl and Yasargil, 1961) were not even specified. The influence of the side or laterality of surgical intervention was defined and analysed in 3 studies only (McFie, 1960; Riklan et al., 1960; Krayenbühl et al., 1965). Moreover, in most cases, the conclusions reached represent extrapolations from a particular surgical technique and target and must therefore be considered of limited generality. (Riklan and Levita, 1969).

McFie (1960) studied 56 Parkinsonians before and immediately after unilateral pallidotomy or thalamotomy (ventro-lateral), and Riklan et al. (1960) carried out a similar study on 71 patients. (Target area in both studies was similar thus their results are comparable). Left hemisphere intervention resulted post-operatively

in significantly reduced performance on "verbal" tests i.e. on arithmetic (McFie, 1960 and Riklan et al., 1960) on digit span (McFie, 1960 and Riklan et al., 1960), on similarities (McFie, 1960), and on vocabulary (McFie, 1960), subtests of the WAIS (McFie) and WBAI (Riklan). Both studies reported that right hemisphere intervention significantly reduced block design performance, although McFie found also some reduction of arithmetic performance. This reduction, however, was not as marked a reduction as that produced by left hemisphere intervention. Considering the reduction in performance of both left and right groups, Riklan et al. found that the "greatest single loss was in verbal IQ for the left brain operates for whom the mean number of points lost was 9.1".

Riklan et al. (1960) carried out a 'long-range' re-test on forty-nine of these patients. At re-test, some nine months post-operatively, no significant difference was found between post-operative subtest scores and "long-range" follow-up scores.

Jurko and Andy (1964) found the reverse. No significant reduction of WAIS scores was found between pre- and immediate post-operative assessment for a group of twenty-one patients. At follow-up assessment of eight patients, one to two years after surgery (posterior ventral thalamus and subthalamic region), a significant decrease in verbal IQ was found. (This appears to be largely attributable to poor performance on the 'similarities' subtest). Unfortunately, however, Jurko and Andy did not consider their results in terms of

hemisphere intervention. They attributed the disparity between their results and the overall findings of other workers to three major factors: a more pronounced post-operative morbidity following surgical techniques other than their own; differences in the timing of follow-up assessment (18 - 24 months for their own as compared, for example, to 4 - 13 months for Riklan et al.); and differences in surgical target (pallidum and VL thalamus for McFie and Riklan et al., PL thalamus and/or subthalamus for Jurko and Andy). There is, of course, one more important difference to add. Jurko and Andy tested 21 patients in the immediate post-operative period (McFie tested 59 and Riklan et al. 71) and 8 at follow-up (Riklan et al. tested 49).

Krayenbühl et al. (1965) in their article "Is there a dominant thalamus?" reported findings substantially different to those already discussed. Ten right-handed patients undergoing 'dominant' surgery and ten undergoing non-dominant surgery were investigated. Surgery target was the posterior ventro-oral thalamic nucleus, and the lesion was made by means of high-frequency coagulation. Krayenbuhl et al. found *no* changes in intellectual abilities after surgery. However, the two patient-groups did react differently on other tests following surgery. Thalamotomy of the dominant hemisphere was associated with post-operative reduction not only of verbal memory, but also, of the capacity for verbal learning. Furthermore, this deficit was unchanged at the six-month follow-up assessment. These patients undergoing

non-dominant surgery showed a significant *improvement* post-operatively. Tests of general information, 'assemblage' and arithmetic reasoning "suggest an effect of post-operative adaptation". Post-operative immediate visual memory also improved significantly.

The two most striking post-operative dysphasic sequelae - naming difficulties and verbal memory deficits - may be induced by electrical stimulation of subcortical structures. Ojeman and Ward (1971) found that stimulation of the left 'dominant' medial central portion of the thalamus evoked alterations in object naming ('anomia') and perseveration. These alterations were obtained neither from stimulation of areas directly superior, inferior, medial or lateral to the medial central portion, nor from stimulation of areas in the right 'non-dominant' thalamus. 'Anomia' was defined by Ojeman and Ward as "the inability to name objects correctly with a retained ability to speak, usually shown by the patient being able to say 'this is a' even though he cound not correctly name the object". The majority of anomic errors evoked by stimulation were misnamings (63 per cent); the remainder were omissions. Misnamings were 'gross errors', e.g. "ace" for 'church'. The patients were not confused, for the incorrect name given was not necessarily the name of an object pictured elsewhere in the test. Similar results had been obtained in an earlier study by Ojeman, Fedio and Van Buren (1968). Stimulation of the pulvinar and *en passage* fibres related to the centrum medianum and dorsomedial nuclei only of the left 'dominant' hemisphere

produced 'anomia'. (These findings are supported by a serial section study by Van Buren and Borke, 1969). Ojeman, Blick and Ward (1971) reported the effect of stimulation of VL thalamus (medial central portions) on a test of short-term verbal memory. Stimulation at the time of recall, with current levels below the threshold for changes in object naming, significantly disturbed recall, while stimulation during the presentation of test material to be recalled later, was associated with a decrease in recall errors in comparison to the non-stimulation conditions. Ojeman and Fedio (1968) noted a similar evoked disturbance of retrieval of verbal material from short-term memory store with stimulation of the pulvinar at equivalent low current levels. Thus there is an overlap between the sites from which changes in object naming and changes in short-term verbal memory can be evoked. Ojeman (unpublished data, cited in Ojeman and Ward, 1971), however, has demonstrated that "this overlap of speech and short-term verbal memory functions at the thalamic level does not seem to be present in the left temporal-parietal cortical area where anomia can be evoked".

Van Buren (1963), although they too obtained similar results of nominal difficulties, memory deficit and confusion when stimulating in and/or near the head of the caudate nucleus, conclude,"...we are left with the impression that what has been produced by stimulation within the vicinity of the head of the caudate nucleus is not indeed aphasia, but a more basic disturbance in which

the impulse to speak or to continue another task has been dulled or forgotten".

This conclusion suggests that what appears at first glance to be a nominal or ("expressive") aphasia is, in fact, a disturbance of a function more closely related to the effector mechanism of speech itself than of language. Although it is conceivable that in a test situation where a patient is asked to name an object correctly within a given time period, an akinetic patient (without being "dysphasic") could indeed fail the test, it is not possible from the limited descriptions contained in published papers to establish whether or not this was controlled for. It would indeed be interesting to know whether, if given time, the patients diagnosed as post-operative 'nominal aphasics' would still be considered such. However, irrespective of whether or not the diagnosis of post-operative dysphasia is a false positive error, the suggestion by Van Buren and his co-workers that nominal difficulties evoked by stimulation are akinetic in nature implies an intimate connection to the phenomena of speech acceleration and of total speech arrest consequent upon subcortical stimulation.

# CHAPTER 5

# METHOD OF INVESTIGATION

## RATIONALE AND EXPERIMENTAL HYPOTHESES

Of the numerous and varied syndromes associated with lesions of the basal ganglia, Parkinsonism was chosen for study. It is the commonest of the syndromes and may reasonably be regarded as the most representative. Furthermore, it affects both sexes from about the fifth decade of life - long after the skills of communication have been established.

Several types or forms of Parkinsonism have been described. For this study two forms were selected: the idiopathic form of the disease, i.e., 'paralysis agitans' and the form known as 'post-encephalitic Parkinsonism'. The pathology of each of the chosen forms has been well documented. Post-encephalitic Parkinsonism is associated with greater neurological damage than is paralysis agitans. Thus these two forms provide scope for investigation not only of the role played by lesions of

the basal ganglia in the disturbance of speech, but also of possible differences between the effects of numerous and diffuse lesions (as in post-encephalitic Parkinsonism) and more circumscribed lesions (as in paralysis agitans). Intuitively one would expect greater speech disturbance to be produced by more extensive lesions.

In the 1960's stereotactic surgery was considered an efficacious method of treatment for Parkinsonism. The surgical procedure involved the stereotactic placement of additional lesions induced by high-frequency waves, extreme cold or heat, etc., in (most commonly) the ventrolateral nucleus of the thalamus and/or the pallidum. There are, therefore a number of patients who, in addition to the Parkinsonian-producing lesions, have these induced sub-cortical lesions. Patients with a history of previous subcortical surgery were included in the study (provided, of course, that their basic Parkinsonian disease was one of the two relevant forms). Extending the hypothesis stated above that 'the more damage to the subcortex the greater the speech disturbance' it was predicted that patients with these additional induced subcortical lesions would have more disturbance of speech than patients who had not undergone this form of treatment.

Another, and extremely important, consideration in choosing to study these forms of basal ganglia disease, was the advent of L-dopa. It has already been pointed out in Chapter 4 that the speech disturbances related to basal ganglia lesions are independent of the two positive

symptoms of subcortical damage, i.e., tremor and rigidity. On these grounds alone there is a *prima facie* case for postulating a connection between speech disorders and akinesia - the remaining symptom of the characteristic Parkinsonian triad. Moreover, when one takes into account the adverse effects of stereotactic surgery in inducing speech disturbances in patients with no pre-operative speech disorder, together with Fagel's claim (1968) that this form of treatment *increases* akinesia, the hypothesis gains stronger foundation. In the past, the relationship between akinesia and speech disturbances has been ignored - perhaps because prior to the recent theories linking dopamine and akinesia it was not readily testable. With the advent of L-dopa, it is now possible to test the hypothesis that dopamine deficiency is implicated in the production of speech disorders in patients with lesions of the basal ganglia.

The present study began soon after Edinburgh had become one of the centres in Britain where L-dopa was available for clinical trial, and it was designed to test the following hypotheses:

1. *The lesions which cause akinesia are responsible for the speech disturbance of Parkinsonian patients.* That is, the speech disturbance is a manifestation of akinesia. The greater the extent of the lesions, the more severe the akinesia and hence the greater the degree of speech disturbance.

2. *The lesions which occasion the speech disturbance are biochemically mediated.* L-dopa has been shown to

ameliorate akinesia; it follows that the amelioration of akinesia by this form of dopamine replacement therapy will be reflected in a diminution of the degree of speech disturbance.

## SELECTION OF SUBJECTS

Apart from the initial decision concerning which forms of the disease to study, the only subject-selection criteria operating were two fortuitous ones. Firstly, since L-dopa is effective in reversing akinesia all patients admitted for L-dopa treatment (and hence all those included in this study) were predominantly akinetic. Secondly, the course of the treatment, coupled with the design of the study, inevitably selected subjects in the following way: the basic design of the investigation was a test-retest procedure - a procedure which has the distinct advantage of allowing each patient-subject to serve as his own 'control'. The experimental design thus served gratuitously to select patients since, to be included in the study, patients had to be tested both before treatment and after treatment, prior to discharge. In practice this meant that those patients who could not tolerate the gradual build-up of dopamine had the treatment withdrawn, and thus could not participate in the investigation. The corollary is also true: those patients included in the study comprised only those who were able to tolerate dopamine, and who,

after about three to six weeks, had shown sufficient improvement on the clinical criteria of the neurologist in charge to be discharged from hospital.

Apart from these two unavoidable selection processes no further selection was made. *In no circumstances was a patient selected because he had normal or because he had disturbed speech.*

## DESCRIPTION OF THE EXPERIMENTAL GROUP

### COMPOSITION

A group of 70 subjects was drawn from the series of Parkinsonian patients consecutively admitted for L-dopa treatment to two local hospitals - the Northern General and the Royal Infirmary. All patients were right-handed, and all of 'normal' intelligence, as measured on the Mill Hill vocabulary scale and Raven's matrices.

Thirty of the patients were relatively young. Of these, twenty-seven had Parkinsonism of long standing together with a clear, unambiguous history of encephalitis. The remaining three had had Parkinsonian symptoms for only a relatively short time, no clear history of encephalitis, and, furthermore, none of the post-encephalitic Parkinsonian symptoms, such as oculogyric crises. The differential diagnosis of paralysis agitans and post-encephalitic Parkinsonism, particularly in the younger patients, is not always

easy. (This problem was discussed in Chapter 1). For the present study a stringent criterion of diagnosis was adopted: only patients with an unambiguous history of encephalitis were considered as being 'post-encephalitic' Parkinsonian patients.

Of the total group of subjects, just under 32% had previously undergone stereotactic surgery. Half of them were found to have paralysis agitans, and the other half, post-encephalitic Parkinsonism.

The subjects were thus subdivisible according to type of Parkinsonism and surgical history:

patients with paralysis agitans who had not undergone surgery (subgroup 'PA', N=32);

patients with paralysis agitans who had undergone surgery (subgroup 'PA+OP', N=11);

patients with post-encephalitic Parkinsonism who had not undergone surgery (subgroup 'PE', N=16);

patients with post-encephalitic Parkinsonism who had undergone surgery (subgroup 'PE+OP', N=11).

The composition of the experimental group reflected well the composition of the general Parkinsonian population. Paralysis agitans is the commonest form of Parkinsonism. Post-encephalitic Parkinsonism, as its name implies, is found amongst those patients who had encephalitis during the post-war epidemics. There is, thus, a finite, and diminishing, population of post-encephalitic patients. In the experimental group, post-encephalitic patients were outnumbered by almost 2:1.

Patients with a (subcortical) surgical history are an even more constrained population. Selection of patients for surgery was a careful process. Age of patient, length of illness, and the severity of (the positive) symptoms were critical factors. In practice this meant that patients with paralysis agitans, because of the relatively recent onset of their symptoms, and patients with post-encephalitic Parkinsonism, because of their relatively young age, were good candidates for surgery. Not surprisingly therefore, comparable numbers of paralysis agitans and post-encephalitic Parkinsonian patients had undergone surgery.

Surgery, however, appears no longer to be the first choice of treatment for Parkinsonism. Doubts as to the long- and/or short-term benefit of surgery, particularly in relation to its side-effects, have been reported with increasing frequency in recent years. The now prevalently cautious attitude to surgery is reflected in the present series of patients: the most recent surgical procedure on any of these patients was carried out in 1968. On average, surgery was undergone 11 years previously. An equal number of left and right procedures were found to have been carried out on the experimental group; and only three patients had had bilateral surgery.

AGE

The average age of the group as a whole, and of the four subgroups are summarized in TABLE 5A. Post-

encephalitic patients were found to be significantly younger than paralysis agitans patients; no difference in age was found between patients who had undergone surgery and those who had not. (see TABLE 5B).

A. MEAN AGE

| SOURCE | MEAN |
|---|---|
| PA | 66.75± 7.83 |
| PE | 60.81± 8.19 |
| PA+OP | 66.82± 4.55 |
| PE+OP | 61.56±12.25 |
| GROUP AS A WHOLE | 64.68± 7.50 |

B. ANALYSIS OF VARIANCE

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 511.37 | 1 | 511.37 | 10.03* |
| SURGERY | 1.45 | 1 | 1.45 | |
| INTERACTION | 1.76 | 1 | 1.76 | |
| ERROR | 3264.30 | 64 | 51.00 | |

*p<.01

TABLE 5

LENGTH OF ILLNESS

Since the disease is progressive, 'length of illness' is an important descriptor of a Parkinsonian population. However, because of the very insidious onset of the disease, it is almost impossible to determine the true duration of the illness. A good estimate of the duration of the illness is provided by the length of time since the onset of the first symptoms.

The experimental group was found to have had

Parkinsonism on average for about 15.66 years. The mean length of illness for each of the four subgroups is contained in TABLE 6 below. As can be seen, paralysis

MEAN LENGTH OF ILLNESS

| SOURCE | MEAN |
|---|---|
| PA | 8.25 ± 3.05 |
| PE | 28.38 ± 12.29 |
| PA+OP | 16.10 ± 5.95 |
| PE+OP | 25.29 ± 9.41 |
| GROUP AS A WHOLE | 15.66 ± 11.04 |

TABLE 6

agitans patients who had undergone surgery had had Parkinsonism for almost twice as long as paralysis agitans patients who had not. Furthermore, the two post-encephalitic patient groups had had Parkinsonism for more than three times as long as the unoperated paralysis agitans patients. As could be anticipated from these figures, the subgroups differed significantly in terms of the average length of illness ($F=29.72$; $d.f.=3,58$; $p<.01$). Multiple comparisons of the four means of length of illness (using Newman-Keuls test) showed that only one pair of means did not differ significantly: there was no difference between the length of illness of the two post-encephalitic subgroups. The mean length of illness for subgroup PA was significantly shorter than that for subgroup PA+OP ($p<.01$); and that both these means were shorter than the means for the two post-encephalitic subgroups ($p<.01$ in all cases).

L-dopa treatment was given to the patients after the initial test-protocol, and other routine tests had been carried out. The drug was administered orally, in gradually increasing amounts until the optimal level for each patient was reached. The optimal level for each patient was assessed in terms of his response to the drug. It represented the maximum dosage a patient could tolerate without developing hyperkinesia and other unwanted side-effects. It took, on average, four weeks for this gradual build-up to maximum dose level to be effected.

The optimal daily dose levels ranged from 1.5 to 10 grammes. TABLE 7 shows the mean daily dose levels.

MEAN OPTIMAL DOSE LEVEL
(GRAMS PER DAY)

| SOURCE | MEAN |
|---|---|
| PA | $3.769 \pm 2.05$ |
| PE | $3.483 \pm 1.08$ |
| PA+OP | $4.420 \pm 1.77$ |
| PE+OP | $3.270 \pm 1.58$ |
| GROUP AS A WHOLE | $3.720 \pm 1.84$ |

TABLE 7

Analysis of variance revealed no significant differences between the four subgroups ($F=0.4713$, $d.f.=3,51$, $p<.01$).

## EXPERIMENTAL TASKS AND MEASURES

The term 'akinesia' was introduced to neurology by Kinnier Wilson. It was also Wilson who introduced the concept of a dual motor system - a pyramidal system that subserves 'voluntary' movement, and an extra-pyramidal system that subserves 'spontaneous' movement. According to Wilson (1925), 'akinesia' affects both 'spontaneous' and voluntary movement. There is general poverty of movement in akinetic patients, and when movement does occur it is characterized by its slowness. Furthermore, an akinetic patient shows a marked lack of 'spontaneity' and 'drive'. In his 1925 article in the Lancet, Wilson avoided actually defining his term, but, from his descriptions of akinetic movement, it appears that akinesia affects two aspects of movement: its initiation is delayed and its description is slow, laborious and minimal.

According to Wilson, *all* movement is affected by akinesia. Thus speech, being a highly complex motor sequence, should show the same two types of disturbance (in initiation and description) as do other movements. Simple tests were constructed to measure these two aspects of disturbance.

Certain constraints on the choice of tasks should be mentioned. Since a test-retest procedure was employed, it was necessary to avoid or minimize unwanted learning or practice effects. This was achieved by the use of

tasks requiring only already highly-practised 'automatic' skills. Such tasks also enjoyed the merit of not tiring the patients and of not being too stressful, a factor of consequence in respect of the more emotionally labile patients.

## MEASURES OF CLINICAL STATUS

**BEFORE TREATMENT STATUS:** On admission to hospital, and before treatment was initiated, each patient was seen by the neurologist in charge, who assessed the clinical status of the patients. The degree of severity of each of the three characteristic Parkinsonian symptoms - tremor, rigidity and akinesia - was rated. A four-point scale was used for tremor and for rigidity (0 = no tremor/rigidity at all; 1 = slight tremor/rigidity; 2 = moderate tremor/rigidity; 3 = severe tremor/rigidity). Since all patients included in this study had some degree of akinesia, only a three-point scale was required in the rating of severity of this symptom (1== slight; 2 = moderate; and 3 = severe). Whether tremor and/or rigidity was manifested bilaterally or on only the left - or right-sided limbs was also noted.

**IMPROVEMENT WITH TREATMENT:** Once a patient had been stabilized on his optimal dosage level of L-dopa, a clinical assessment of the change in akinesia was made by the same neurologist. Clinical improvement was

rated on a five point scale (0 = minimal, if any, improvement; 1 = slight improvement; 2 = moderate improvement; 3 = marked improvement; 4 = excellent improvement).

Patients who had shown either clinical deterioration or no clinical change were excluded from the present investigation. Only those patients who were able to tolerate large enough levels of L-dopa to effect clinical improvement without suffering side-effects were included. All patients rated 1 - 4 met this requirement, and an extremely small number of patients initially considered suitable candidates for L-dopa treatment, and hence possible candidates for this investigation were encountered.

## MEASURES OF MOTOR ABILITY

A number of short and easy-to-administer motor tests have been used by other workers to measure the effects of L-dopa. These tests, however, tend to be based on simple motor activity (for example, the digital counting method used by Mawdsley et al. (1972)), which is not comparable with the highly complex movements that form the basis of speech.

Handwriting is a complex yet highly-practised motor skill. It provides a highly appropriate material in which to detect motor improvement since it is generally

agreed that writing is adversly affected by akinesia. The writing of akinetic patients is generally small, and frequently, becomes progressively smaller, both horizontally and vertically.

Patients were asked to write their full name, address, some numbers (46,573,1,001) and a sentence ('Many women went to market.') on a blank sheet of paper with a self-sharpening propelling pencil. The instructions followed the general form: "I want you to write your name and address. As soon as I say 'Begin!' you can start.". Three measures were derived from this task:

**SIZE OF WRITING:** The length of each word was measured in centimetres and a mean for each patient's writing under test and retest conditions was calculated.

**TIME TAKEN TO WRITE:** The time each patient took to write his name and address was measured with a 1/100th sec. stopwatch, taking care not to let the patient see he was being timed. Timing started at the first stroke the patient executed, and ended with the last full stop.

**TIME TAKEN TO START WRITING:** The time that elapsed between the command 'Begin!' and the first stroke the patient executed was also measured. A second stopwatch (also calibrated to 1/100th sec.) was used, and care was taken to ensure that the timing was conducted unobtrusively.

Responses for the measurement of continuous speech were recorded on magnetic tape. The procedure for recording was designed so as to strike a balance between two rather different requirements. On the one hand, recordings suitable for subsequent use with automated analyses employing 'voice keys' had to be made. On the other hand, it was extremely desirable to obtain realistic examples of how patients usually spoke. It was feared that constructing too formal a recording session in the only available sound-proofed laboratory which was situated some miles from the hospital perhaps would influence patients to talk uncharacteristically well, and produce loud, over-articulated, laborious speech. It was, therefore, decided to make the recordings at the hospital, in a room near the wards, and that the sessions be structured in as informal a manner as possible with minimal attention being drawn to the process of recording.

A Revox (model A77) tape recorder was used. Only clean, new tapes (BASF low-noise SP5Z) were employed. The recordings were made at 7½ inches per second, and only one of the two available tape-tracks (the lower) was used, to avoid any cross-image due to tape deterioration. Input was through a boom-mounted headset-microphone (Sharpe, Mark II LM) to ensure a standard mouth-microphone distance even in patients with severe

head tremor.

The microphone used was uni-directional. The use of this type of microphone was well rewarded. It effectively failed to record not only any general background noise of the hospital, but also the rustles and noises produced by tremulous limbs. Later oscillographic analysis showed that the recordings made under the hospital conditions had a signal-to-noise ratio of at least 10db, and that the recordings were not appreciably worse than those made under laboratory conditions.

The procedure for calibration of input level to the tape recorder was similar to that used by Canter (1966). A standard acoustic stimulus was recorded just prior to the speech recording for each subject was made. The 1,000 cps output of an Advance signal generator was fed into the tape recorder. The voltage was 0.1 volts, measured on a Marconi valve voltmeter. The tape recorder gain control was set so that the input signal gave a reading of zero on the VU meter built into the tape recorder. The input tone was recorded for 30 secs. The tape recorder gain control was not altered throughout the recording session of a given patient. The procedure was repeated for each individual recording session.

TASK: CONVERSATION

This was the first speech sample that was recorded. It was initiated by general questions from the examiner,

and usually was confined to topics such as the patient's family (frequently concerning grandchildren), occupation, particular interests, or, as a last resort, how the patient spent his time in hospital. In general, the experimenter tried to keep her contribution to the conversation to a minimum while at the same time eliciting fairly long, uninterrupted samples of the patient's speech. It was not a difficult situation to engineer - once an appropriate topic was found, the patients proved quite loquacious.

The purpose of this task was twofold: to minimize the inhibitions attendant on the test and recording situation, and to obtain a sample of conversational speech which would later be used by the judges for evaluation.

TASK: AUTOMATIC SPEECH

Patients were asked to recite the alphabet, the names of the days of the week and the months of the year. They were also asked to count from 1 to 10. The instructions for this task were non-commital. No reference to either rate or loudness of utterance was made. Patients were merely told, for example: "I want you to count from 1 to 10. As soon as I say 'Begin!', you can start."

Two measures of temporal aspects of speech, both requiring similar analyses, were based on the recordings of the patients' counting. The reasons for choosing this

particular activity for analysis are several: In counting from 1 to 10, the number names, with the sole exception of 7, are monosyllabic. Counting is a universally familar activity, and it conforms to Hughlings Jackson's 'inferior' or 'automatic' speech. It is, therefore, virtually free of those hesitations consequent upon the formation of 'superior' or 'propositional' speech which has been extensively studied by Goldman Eisler (1968). Furthermore, in the act of counting, syntactical and other paralinguistic markers do not constrain the rhythm of speech.

The speech samples were played into a signal detector (FIGURE 16) which was turned on by the

SIGNAL DETECTOR

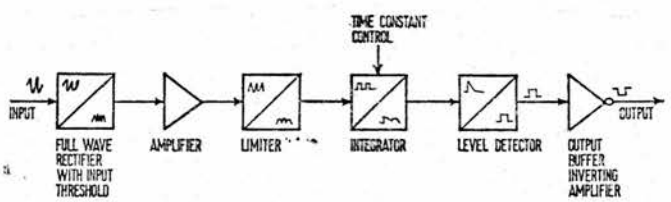



FIGURE 16

beginning of phonation and off by the cessation of phonation. The output of the detector was fed to a chart recorder (Bryans modal 27000) and a graph of the on/off activity of the detector was obtained. In order to monitor that the detector was responding to as much of the phonation as was possible, outputs from both the tape recorder and signal detector were fed to a two-channel storage oscilloscope. The gain controls on the tape recorder and signal detector were adjusted so that the detector could be seen (on the oscilloscope) to respond to the extreme beginning and end of each phonation. This required delicate adjustments of the gain controls. In general, the most satisfactory results were obtained when the output gain from the tape recorder was set relatively high, and the input gain to the signal detector relatively low. The controls were adjusted for each speech sample that was analysed.

PERIODICITY OF PAUSE AND PHONATION: The length of phonation for each of the ten digits (i.e. the length of the "on" phase of the signal detector) and the length of the nine intervening pauses (i.e., the length of the "off" phase of the signal detector) was measured directly from the chart recordings. When, as occasionally occurred, two phonations ran together without detectable pause, the total phonation time was halved and this value was allotted to each digit. Means and standard deviations for the duration of phonation and pause were calculated for each patient under test and retest conditions.

REGULARITY OF SPEECH: For this analysis, the counting activity was considered as a sequence of 'word pause' units. If speech were of even pace or rhythm, each unit would be of comparable duration. In festinant speech, the units later in the sequence would be shorter than units earlier in the sequence. The digit 'ten' was excluded from the analysis. The length of each unit (i.e., each word and its following pause) was measured from the chart recording.

TIME TAKEN TO START 'AUTOMATIC' SPEECH: The time that elapsed between the command 'Begin!' and the beginning of the utterance of the first unit in the sequence - digit, name of weekday, name of month, letter of the alphabet, were all measured using the voice key and chart recorder. A mean initiation time based on all four measures was calculated for each patient under both test and retest conditions.

TASK: READING

The passage chosen for this task was 'Arthur the Rat'. The passage is a narrative, and is characterized by a predominance of high-frequency vocabulary. It was felt that these two factors were an advantage and would perhaps produce less errors in reading than, say, the highly descriptive more abstract 'Rainbow Passage' developed by Fairbanks.

The patients were first given the printed copy of

the reading passage to look over. When they were satisfied it presented no difficulty, they were asked to read the passage aloud. (To ensure that the patients were not unduly hurried, the experimenter would give the patient the printed copy, and instead of sitting, clearly waiting for the patient to finish looking over the passage, the experimenter used this time to fill in details of the patient's case history from his case notes.)

The instruction for the task, as advocated by Johnson et al. (1963), were non-commital: patients were merely asked to read 'as you ordinarily would'. No more detailed instructions were given.

Two measures were based on this reading task:

RATE OF READING: The time taken to read the passage was measured using a 1/100th sec. stopwatch. The number of words read per minute was calculated for each patient under both test and retest conditions.

VOICE VOLUME: The reading sample was used for the voice-volume measures. "Loudness" is a psycho-accoutic concept, and unfortunately as yet there is neither a satisfactory nor a standard means of adequate quantification. In this study the basic technique suggested by Mr. Antony of the Linguistics Department (Edinburgh Univ.) and used by Allan et al.(1966), and Hermann et al.(1966) was used, with some modification. Antony's technique involves feeding a speech sample into a simple form of sound level meter with a scale in

decibels instead of volts. The meter thus measures amplitude of the input signal, at 5 sec. intervals. For this study, the input-level of the signal was standardized by means of the calibration tone preceding each recording. The output gain of the tape recorder was adjusted so that when the recorded tone was played through a chart recorder (Bryans) a linear excursion of comparable amplitude for each recording was obtained. Once the gain was satisfactorily adjusted, it was not altered and, on this gain setting, the reading sample was played into the sound level meter. Mean db measures for each patient under both test and retest conditions were calculated.

TASK: SUSTAINED PHONATION

For this item the patient was required to say the sound "ah" for as long as possible, without undue strain. After a demonstration by the investigator, the test was carried out, measuring the length of the phonation with a 1/10th second stop watch. This test was performed at three stages of the test-session - at the beginning, middle, and end; a mean-length of phonation was calculated.

MEASURES OF CONTINUOUS SPEECH - NON-PARAMETRIC

The recorded samples of the patients' conversation,

'automatic' speech sequences and reading were played to two judges for evaluation. Both judges were experienced in assessing disturbed speech.

Construction of the rating-scales.

The judges, together with the writer, selected five variables, which, on the basis of their clinical experience were believed to comprehensively cover those aspects of speech disturbance relevant in Parkinsonism. The variables were agreed by all three to have the following scope of reference:

'INTELLIGIBILITY': a measure of the adequacy of speech for everyday communication;

'DYSARTHRIA': a measure of the clarity, precision and to some extent, the speed of articulation:

'PROSODY': a measure of stress and intonational patterns;

'FESTINATION': a measure of that temporal disorder peculiar to Parkinsonism - the hurrying at the end of an utterance; and,

'PHONICS': a measure of vocal quality based on such factors as pitch, timbre, and, to some extent, loudness of voice.

It was agreed that each parameter would be represented by a five-point scale of severity of disturbance. A seven-point scale would call for unnecessarily fine, and perhaps impossible, discrimination, while a three-point scale would involve too gross and inflexible a classificatory model. A

rating-score of '1' represented 'slight impairment'; '3', 'moderate impairment'; and, '5' 'marked or severe impairment'. Rating scores of '2' and '4' represented intermediate degrees of impairment. If no disturbance was heard by the judge/s, the sample received no rating-score.

Procedure

The speech samples were randomly assigned in groups of ten recordings. The samples were not re-recorded; the original recordings were played to the judges for evaluation so that no difficulties with artificial reduction of the signal-to-noise ratios of the tapes would be encountered.

One group of ten speech samples was played at each rating-session. The same Revox tape recorder that the tapes had been made on was used. The playback volume was kept constant throughout each and every session. (The volume control knob was set to level 7). The rating-sessions lasted roughly 1 - 1½ hours. The judges were not told the name of the patient whose recording was being played, nor did the judges have information as to whether they were listening to a 'before' or 'after' treatment recording. Judges were free to ask for the recording under consideration to be replayed as many times as necessary for them to make their evaluations; they were not allowed to hear the previous recordings for comparison. There was no collaboration or discussion between judges during the rating-sessions.

Reliability of assessments

Ten speech samples had, unknown to the judges, been presented twice for evaluation. The differences between the two sets of ratings each judge had awarded these samples were tested to provide a measure of rating consistency, or *'intra-judge reliability'*. Wilcoxon's matched-pairs signed-ranks test was used for this purpose. In no case did the difference between two sets of ratings even approach significance at the .05 level, indicating a high degree of intra-judge reliability.

A high degree of *inter-judge* agreement on each scale was also found. TABLE 8 presents the values of

INTER-JUDGE RELIABILITY

| SCALE | PRE | | POST | |
|---|---|---|---|---|
| | τ | z | τ | z |
| 'OVERALL' | 0.717 | 6.859 | 0.677 | 6.479 |
| 'DYSARTHRIA' | 0.631 | 6.036 | 0.751 | 7.188 |
| 'PROSODY' | 0.743 | 7.110 | 0.663 | 6.345 |
| 'FESTINATION' | 0.730 | 6.987 | 0.698 | 6.690 |
| 'PHONICS' | 0.610 | 5.838 | 0.621 | 6.607 |

TABLE 8

Kendall's rank order test together with their associated z-scores. A z-score of 1.64 is associated with the .05 level of probability. As can be seen from TABLE 8 a highly significant level of agreement was revealed in the assessment of speech, on all five scales.

Two of the three measures of the time taken to begin a complex sequence of movement - TIME TAKEN TO START WRITING and TIME TAKEN TO START 'AUTOMATIC' SPEECH SEQUENCES - have already been described. The third measure, described below, was based on performance of a confrontation naming task.

The Oldfield & Wingfield Object Naming Test (1965) was used. The test materials comprise 36 cards each bearing an outline drawing of an object. (see FIGURE 17

EXAMPLES OF STIMULUS MATERIAL (REDUCED IN SIZE)

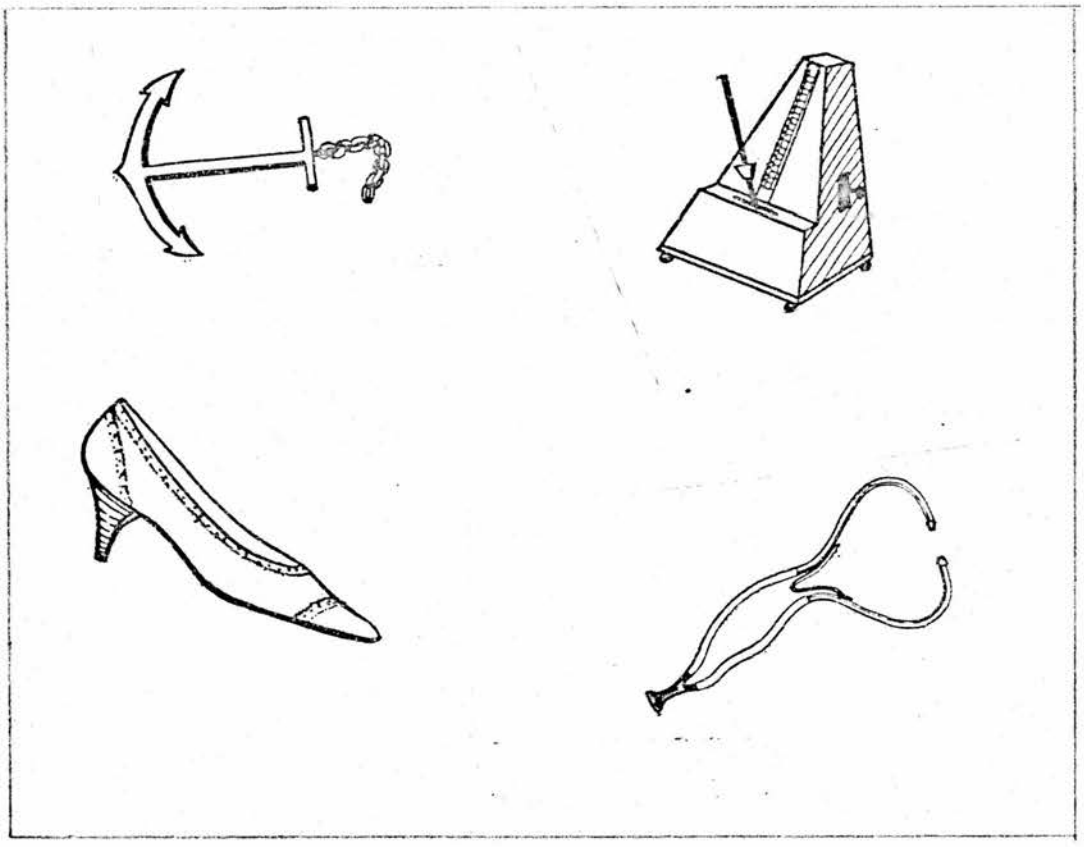


FIGURE 17

for four examples of the drawings used in the test). The depicted objects were chosen by the test constructors so that the frequencies of their name-words, as given in the Thorndike-Lorge (1944) word count, were spread through a wide range, i.e., from 'AA' words with a frequency of occurrence of >100 per million down to words with a frequency of <1 per million. Ten of the outline drawings are for practice, although the subject does not know that his responses to them will be ignored.

The test was administered as advocated by Oldfield and Wingfield (1965): The subject was told he would be shown a series of cards, and that each card had on it a drawing of an object. He was instructed to name the object as *quickly* as he could, giving its common name without qualification or further description. To illustrate the instructions, he was given three examples of naming common objects in the experimental room ('bag'; 'window'; 'door'). Before the test began it was once again stressed that he was to respond *as quickly as possible.*

The following procedure was used: with the experimenter seated opposite the subject at a table, each card in the pack was flicked over while an electronic timer (Advance TC 14) was started at the same instant. As soon as the subject responded with the correct name the timer was stopped. Response-latency was measured in msecs., and verbatim records of the patients' responses were made.

The cards were presented to the patients in one of the three (random) orders described by Oldfield and Wingfield (1965), with the constraint that no patient be exposed to a particular order more than once.

## MEASURES OF ABILITIES WITH POSSIBLE RELEVANCE TO CONFRONTATION NAMING

A number of standard psychological tests were administered to the experimental group. The tests were chosen for their relevance to measure those psychological functions that one intuitively believes to be related to the functions or abilities involved in a confrontation naming task. The tests used were:

**BLOCK DESIGN:** The Block Design subtest of the Wechsler Intelligence Scale was used. In this task, derived from Kohs' Block test, which was intended to measure intelligence (Kohs, 1923), the subject is asked to copy a red and white patterned drawing using three-dimensional blocks. Time limits are set and time bonuses can be gained for the more difficult nine-block designs. A pilot study revealed that even severely akinetic Parkinsonian patients were capable of completing the more difficult items within the time limits required to earn maximum time bonuses. There are six four-block and four nine-block designs. The maximum score is 48. Since performance on this test is influenced by the age of the

subject, the raw scores were corrected for age according to the tables supplied with the W.A.I.S. and these age-corrected scores formed the basis of all result analyses.

SPAN OF APPREHENSION: The 'digit span' subtest of the Wechsler Memory Scale was used. The scale offers two versions (Forms A and B), and thus is suited for use in a test-retest experimental design. The test resembles closely the 'digit span' subtest of the W.A.I.S. It comprises two parts - the first requires the subject to repeat an increasing series of digits in the order of presentation ("Digits Forwards"); and, the second, to repeat an increasing series of digits in a reversed order ("Digits Backwards"). The maximum number of digits presented under each condition is eight; the maximum score on the test is thus 16. Since the performance on this test is influenced by the age of the subject, the raw scores were corrected for age according to the tables supplied with the W.A. I.S., and these age-corrected scores formed the bases of all result analyses.

STORY RECALL: The "Logical Memory" Subtest of the Wechsler Memory Scale (Forms A and B) was used. This subtest comprises two short narrative stories. The subject is instructed to listen carefully to the stories which are read aloud by the experimenter. Immediately after both stories had been read, the subject is asked to recall as much of each story as he could. ('SHORT-TERM' MEMORY).

An hour later, without prior warning, the subject was asked once again to recall each story ('DELAYED RECALL'). Half of the subjects were given Form A before treatment and Form B after treatment; the other half vice versa.

# CHAPTER 6

# RESULTS I: CLINICAL STATUS AND MOTOR PERFORMANCE

In this chapter the status of the experimental group both before and after treatment is considered. Two bodies of data are presented: ratings of the clinical status of each patient, by the neurologist in charge, and measures of motor performance, based on handwriting. The former are non-parametric in nature; the latter, parametric.

## METHODS OF ANALYSIS

### NON-PARAMETRIC DATA

The clinical ratings of severity for each of the three characteristic Parkinsonian symptoms - tremor, rigidity and akinesia - provided a picture of the before treatment status. Each of these sets of data was analysed to see whether different degrees of subcortical

damage (represented by the four subgroups) were associated with different degrees of severity of symptoms. A four-point scale had been used in rating the severity of tremor and rigidity. However, it was not possible to subject the data to $\chi^2$ analysis in the form of 4 x 4 matrices (i.e. four degrees of severity x 4 subgroups). For the $\chi^2$ test to be reliable no more than 20% of the cells may have an expected frequency of less than 5 (Siegel, 1956). Neither of the two sets of ratings met this requirement. Consequently the data had to be conflated, in both the row and the column classifications, into 2 x 2 contingency tables. The experimental hypotheses, and the nature of the information, determined the way in which the data was conflated.

Of chief interest were a) whether paralysis agitans patients were less affected than post-encephalitic patients and b) whether unoperated patients were less affected than operated patients. Two separate $\chi^2$ tests were thus required. For one test the rows of the contingency table comprised the patients grouped according to type of Parkinsonism (i.e. PA and PA+OP subgroups versus PE and PE+OP subgroups). For the other, the rows represented patients grouped according to surgical history (i.e. PA and PE subgroups versus PA+OP and PE+OP subgroups). In each test the columns comprised the four degrees of severity conflated to produce two groups of patients rated either as 0 ('no symptom at all') or 1 ('slight'), and as 2 ('moderate') or 3 ('severe').

The situation was slightly different for akinesia. Since all patients in the experimental group were admitted to hospital specifically for L-dopa treatment, it was only to be expected that *all* patients would have some degree of akinesia. A rating category of 0 was therefore not applicable in respect of this symptom. Only three degrees of severity were required to describe the patients (1='slight', 2='moderate', 3='severe').

As was the case with tremor and rigidity, the data did not meet the statistical requirements for expected frequencies so that once again a 2 x 2 contingency table was used. The classification of patients in the rows remained the same as that described above for tremor and rigidity. The column classification, however, represented the data as follows: in one column were grouped all patients rated 1 ('slight') or 2 ('moderate') and in the other all those rated 3 ('severe'). Thus, when the data on akinesia was subjected to the two $\chi^2$ tests, the relative proportions of severely akinetic patients to slightly or moderately akinetic patients was tested.

The data collected from the assessment of clinical improvement was also based on a four-point scale (1='slight' improvement, 2='moderate' improvement, 3='marked' improvement, 4='excellent' improvement). This data, too, did not meet the requirements for expected frequencies and had to be conflated for the two $\chi^2$ tests. In each case the row classification was the same as that used in treating the data on severity of symptoms, as

described above. The column classification, however, reduced the data as follows: in the one column the total number of patients showing a slight to moderate improvement was recorded, and in the other the total number of patients showing a marked to excellent improvement. On the basis of these tests it was possible to establish whether either of the types of Parkinsonism and whether either of the kinds of surgical history were associated with greater degrees of improvement.

PARAMETRIC DATA

The analysis of the three measures of motor function are also contained in this chapter. These measures are: TIME TAKEN TO START WRITING, TIME TAKEN TO WRITE and SIZE OF WRITING. All three sets of measures were parametric in nature, and were analysed according to the following methods:-

In order to see (both before and after treatment) whether the degree of subcortical damage (represented by the four subgroups) was associated with different levels of performance, the data was subjected to analysis of variance. A two (fixed) factor model of analysis was used so that it was possible to test the effect both of type of Parkinsonism and of surgical history. Where appropriate a similar two factor analysis of covariance was conducted in which the after treatment data was adjusted in terms of the before treatment data. Direct inter-group comparisons were carried out where necessary.

One tailed t-tests for independent samples were used.

The differences between the before and after treatment data were tested by means of t-tests (for paired samples). It was predicted that dopamine replacement therapy would improve performance; one-tailed tests were therefore used.

## CLINICAL STATUS

### SEVERITY OF SYMPTOMS BEFORE TREATMENT

On admission to hospital each patient was seen by the neurologist in charge who rated the severity of the patient's tremor, rigidity and akinesia.

DISTRIBUTION OF RATINGS OF TREMOR

| | DEGREE OF DISTURBANCE | | | |
|---|---|---|---|---|
| | 'none' | 'slight' | 'moderate' | 'marked' |
| PA | 17% | 33% | 40% | 10% |
| PE | 36% | 36% | 28% | - |
| PA+OP | 66% | 17% | 17% | - |
| PE+OP | 66% | 17% | 17% | - |
| GROUP AS A WHOLE | 32% | 30% | 30% | 6% |

TABLE 9

TABLE 9 shows the distribution of ratings for tremor. The median of the ratings for tremor for the group as a whole was 1.09, representing 'slight' degree of tremor.

The medians for the four subgroups were also calculated: subgroup PA=1.5, subgroup PE=0.88, subgroup PA+OP=1.00, subgroup PE+OP=1.00. All four medians represent a 'slight' degree of tremor. Not surprisingly, neither of the $\chi^2$ tests to which this data was subjected revealed significant inter-subgroup differences. Paralysis agitans and post-encephalitic patients had similar degrees of tremor ($\chi^2$= .0219; d.f.=1; p>.05). Operated and unoperated patients were also shown not to differ in terms of severity of this symptom ($\chi^2$=.2996; d.f.=1; p>.05).

The distribution of ratings for degree of rigidity is contained in TABLE 10. The group's median rating for

DISTRIBUTION OF RATINGS OF RIGIDITY

| | DEGREE OF DISTURBANCE | | | |
|---|---|---|---|---|
| | 'none' | 'slight' | 'moderate' | 'marked' |
| PA | 23% | 17% | 43% | 17% |
| PE | 36% | 36% | 28% | - |
| PA+OP | 25% | - | 75% | - |
| PE+OP | 50% | - | 25% | 25% |
| GROUP AS A WHOLE | 29% | 18% | 41% | 12% |

TABLE 10

rigidity was 1.5, representing a 'moderate' degree of rigidity. For subgroup PA the median rating was found to be 1.93 ('moderate'), subgroup PE, 0.88 ('slight'), subgroup PA+OP, 1.85 ('moderate'), and subgroup PE+OP, 2.0 ('moderate'). No significant difference was found

between the severity of rigidity shown by paralysis agitans patients and by post-encephalitic patients ($\chi^2$=2.1039; d.f.=1; p>.05) nor between operated and unoperated patients ($\chi^2$=0.0565; d.f.=1; p>.05).

The question of laterality of tremor and rigidity was considered. The majority of patients had bilateral tremor and/or rigidity. The patients with only unilateral 'positive' symptoms were about equally divided as between left-sided and right-sided symptoms. The relative proportions of patients with unilateral left- or right-sided symptoms were similar in all four subgroups.

Thus, although the patients are subdivided into four subgroups according to type of Parkinsonism and surgical history, it was found that:

a) the proportions of patients with bilateral, with left- and with right-sided tremor and/or rigidity were similar in all four subgroups;

b) in general, the patients had only a 'slight' degree of tremor. No differences in degree of tremor were found between the two types of Parkinsonism or the two surgical histories;

c) the patients had a 'moderate' degree of rigidity. No differences in degree of rigidity were found between the two types of Parkinsonism nor between patients who had and those who had not undergone surgery.

Although it is extremely gratifying, from the point of view of experimental design, that the experimental group, selected in as random a manner as possible,

provided four subgroups so homogeneous in clinical features, this very homogeneity in degree of the 'positive' symptoms, i.e. tremor and rigidity, is itself of intrinsic interest. Since stereotactic surgery is performed specifically to 'relieve' or 'reduce' rigidity and tremor, one would have expected patients who had undergone this form of treatment to have a less marked degree of tremor and/or rigidity than patients who had not undergone surgery. However, since both paralysis agitans and post-encephalitic Parkinsonism are progressive degenerative diseases, in evaluating the significance of the findings one must take cognisance of both the length of illness at the time of surgery and the length of illness at the beginning of this investigation.

When this is done, it is seen that paralysis agitans patients confirmed expectations. At the time when paralysis agitans patients underwent surgery, they had, on average, had the disease for roughly 6.1 years. The unoperated paralysis agitans patients had had the disease for an average of 8.25 years. Thus the two paralysis agitans groups are roughly comparable in these terms. When the investigation began, operated paralysis agitans patients had had the disease for an average of 16.1 years. This is almost twice as long as the unoperated patients. (As pointed out in Chapter 5, the difference in length of illness between these two paralysis agitans groups is significant.) The findings, then, that operated and unoperated patients have similar degrees of rigidity and/or

tremor appears to support Gillingham's assertion (1969): "... there is no longer any serious doubt, if we study patterns of daily activity before operation and during follow-up of 10 years or more, that in an increasing number of patients the progress of the disease appears to have been greatly slowed down or even halted."

The results from the two post-encephalitic groups, however, are quite different. Subgroups PE and PE+OP had had the disease for a comparable length of time (see Chapter 5) when this investigation began. Since subgroup PE+OP patients had undergone surgery eleven years previously, that is, after having had the disease for 15.29 years, one would have expected these patients to have a less marked degree of tremor and/or rigidity than their unoperated counterparts, subgroup PE, who had had the disease for 28.38 years. However, no such difference was found. Operated and unoperated patients were found to have symptoms of like severity.

Two explanations could be advanced for this finding: that surgery does not benefit post-encephalitic Parkinsonism, or that the effects of surgery wear off. However since studies have shown that surgery *does*, if only in the short-term, reduce symptoms of post-encephalitic Parkinsonism, the first explanation cannot be sustained. The second explanation, that the effects of surgery are of limited duration, appears the more attractive of the two. Hypothesising that paralysis agitans and post-encephalitic Parkinsonian patients

respond differently to surgery is not unreasonable: the two forms of the disease are known to be of different pathogenesis and their clinical pictures differ in many respects. A differential response to treatment would therefore not be surprising.

What is particularly interesting, however, is the implication regarding the therapeutic nature of surgery. On the basis of follow-up studies of patients 10 years after surgery, Gillingham noted (1969) a sustained reduction in the severity of the positive symptoms of his operated patients. He interpreted these results as an indication that induced pallidal and/or thalamic lesions (at best) halt or (at least) slow down the progression of the disease process. However, the present results from comparisons between operated and unoperated patients after a similar period suggest that some modification of this view of the therapeutic nature of surgery is required. On comparing only post-encephalitic patients, matched in terms of age and date of onset of the disease, no difference in the severity of the symptoms was found between patients who had undergone surgery 11 years previously and unoperated patients. These results suggest that rather than affecting the progression of the disease, the induced lesions have the effect of suppressing the positive symptoms. Once the potency of the induced lesions abates the symptoms manifest with a degree of severity compatible with the stage of development of the disease process. This point clearly needs further

investigation.

The distribution of ratings for degree of akinesia is contained in TABLE 11. The median rating for the group as

DISTRIBUTION OF RATINGS OF AKINESIA

| | DEGREE OF DISTURBANCE | | |
|---|---|---|---|
| | 'slight' | 'moderate' | 'marked' |
| PA | 3% | 29% | 68% |
| PE | 8% | 38% | 54% |
| PA+OP | 17% | - | 83% |
| PE+OP | - | 17% | 83% |
| GROUP AS A WHOLE | 5% | 27% | 68% |

TABLE 11

a whole was 2.84 which represents a 'severe' degree of akinesia. The median rating for subgroup PA was 2.76 ('severe'), for subgroup PE, 2.57 ('severe'), for subgroup PA+OP, 3.5 ('severe'), and for subgroup PE+OP, 3.5 ('severe'). Paralysis agitans and post-encephalitic patients were found to have similar degrees of akinesia ($\chi^2$=0.5263; d.f.=1; p>.05). Operated patients, however, were found to be more severely akinetic than unoperated patients ($\chi^2$=5.6821; d.f.=1; p<.05). This finding strongly supports Fagel's claim (1968) that stereotactic surgery has the undesirable effect of increasing akinesia. It is particularly interesting that this effect is still so evident eleven years after surgery had been undergone.

CLINICAL IMPROVEMENT WITH TREATMENT

Once a patient had been stabilized on his optimal dosage level, a clinical assessment of his condition was carried out by the neurologist in charge. TABLE 12 shows

DISTRIBUTION OF RATINGS OF CLINICAL IMPROVEMENT

| | DEGREE OF IMPROVEMENT | | | |
|---|---|---|---|---|
| | 'slight' | 'moderate' | 'marked' | 'excellent' |
| PA | 10% | 30% | 53% | 7% |
| PE | 59% | 25% | 8% | 8% |
| PA+OP | 14% | 57% | 15% | 14% |
| PE+OP | 50% | 37% | - | 13% |
| GROUP AS A WHOLE | 26% | 33% | 32% | 9% |

TABLE 12

the distribution of ratings of improvement for the group as a whole, and for the four subgroups (in percentages). The medians for these ratings were calculated. The group as a whole were found to have made a 'moderate' improvement (median = 2.21). The median for subgroup PA was 2.56, for subgroup PE, 1.36; for subgroup PA+OP, 2.38; and, for subgroup PE+OP, 1.50. Of the four subgroups, the paralysis agitans patients were found to have shown greater improvement than the post-encephalitic patients ($\chi^2$=6.6842; d.f.=1; p<.01). Surgery, however, did not appear to limit the degree of improvement : operated patients showed a degree of improvement similar to that shown by non-operated patients ($\chi^2$=2.4494; d.f.=1; p>.05).

## MEASURES OF MOTOR PERFORMANCE

### TIME TAKEN TO START WRITING

The latency for writing on command was taken for each patient. The mean value of these latencies for the group as a whole was 1.27±.69 seconds. TABLE 13A contains the mean latencies for the four subgroups.

Analysis of variance showed that the magnitude of the latency for writing on command did not vary with surgical history. Operated and unoperated patients responded comparably. A significant variation, however, was found with type of Parkinsonism ($F=5.39$; $d.f.=1; 30$, $p<.05$). Paralysis agitans patients responded far quicker than post-encephalitic Parkinsonian patients (TABLE 13B).

After treatment, the mean latency for the group as a whole was 1.01±41 seconds. These mean latencies for the four subgroups are also contained in TABLE 13A. Analysis of variance after treatment showed that although the magnitude of latency did not vary with surgical history, it did vary significantly with type of Parkinsonism. Paralysis agitans patients still responded quicker than did post-encephalitic patients (TABLE 13C).

Comparisons between the before and after treatment latencies for writing on command were carried out by means of t-tests for dependent (paired) samples. It was found that the group as a whole was considerably faster after treatment ($t=3.499$; $d.f.=37$; $p<.005$). As can be seen

## TIME TAKEN TO START WRITING

### A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD.DEV. | MEAN | STD.DEV. | | |
| PA | 1.09 | 0.42 | 0.84 | 0.24 | 17 | 2.8402** |
| PE | 1.55 | 0.72 | 1.23 | 0.47 | 7 | 3.6666** |
| PA+OP | 1.10 | 0.25 | 1.07 | 0.20 | 6 | 0.2800 |
| PE+OP | 1.83 | 1.42 | 1.09 | 0.77 | 4 | 0.4885 |
| GROUP | 1.27 | 0.69 | 1.01 | 0.41 | 37 | 3.4490** |

### B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 2.7416 | 1 | 2.7416 | 6.3547* |
| SURGERY | 0.2372 | 1 | 0.2372 | 0.5498 |
| INTERACTION | 0.0097 | 1 | 0.0097 | 0.0225 |
| ERROR | 14.6685 | 34 | 0.4314 | |

### C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 2.4952 | 1 | 2.4952 | 7.1570* |
| SURGERY | 1.1207 | 1 | 1.1207 | 3.2145 |
| INTERACTION | 0.1991 | 1 | 0.1991 | 0.5711 |
| ERROR | 11.8537 | 34 | 0.3486 | |

### D. ANALYSIS OF COVARIANCE

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.3859 | 1 | 0.3859 | 3.3181 |
| SURGERY | 0.4803 | 1 | 0.4803 | 4.1298* |
| INTERACTION | 0.0001 | 1 | 0.0001 | 0.0009 |
| ERROR | 3.8387 | 33 | 0.1163 | |

TABLE 13

from the last column in TABLE 13A, only the two unoperated subgroups, i.e. subgroup PA and subgroup PE, showed a significant change with treatment. In each case, the patients responded faster after treatment. The two operated subgroups, however, showed no significant change with treatment.

These results suggest that change in performance with treatment is strongly dependent on surgical history. To confirm this, the before and after treatment latencies were subjected to an analysis of covariance (TABLE 13D). It was found that when a linear adjustment is made for the effect of variation due to differences in latencies prior to treatment, as measured by the covariate, there *is* a statistical difference between the amount of change shown by unoperated and operated patients. However, no statistical difference was also found between the amount of change shown by paralysis agitans and post-encephalitic patients.

From these results two conclusions may be drawn. On the one hand it is apparent that the magnitude of the latency for writing on command varied significantly with type of Parkinsonism. Paralysis agitans patients respond significantly faster than do post-encephalitic patients. Furthermore, this differential effect of type of Parkinsonism is evident both before and after treatment. On the other hand, it is apparent that a diminution of the magnitude of the latency for writing on command is observed with L-dopa treatment. However, not all four

subgroups show this improvement. Only unoperated patients are faster in responding after treatment. Patients with a surgical history show no significant change in response speed; they are neither faster nor slower with treatment.

SIZE OF WRITING

Before treatment, the average size of words written was 4.2 cms. long, for the group as a whole. The mean sizes of writing for the four subgroups are contained in TABLE 14A. Analysis of variance of the before treatment data revealed no difference in size of writing between the paralysis agitans and the post-encephalitic patients. A significant difference, however, was found between the size of writing of the operated and unoperated patients ($F=7.3729$; $d.f.=1,36$; $p<.05$). (See TABLE 14B). Patients who had not undergone surgery wrote significantly larger than patients who had. In the case of post-encephalitic patients this difference was particularly striking: unoperated patients wrote almost twice as large as operated patients. This difference is highly significant ($t=+3.0024$; $d.f.=13$; $p<.002$).

Comparisons between the before and after treatment measures of size of writing revealed that for the group as a whole there was a significant increase in the size of writing following treatment ($t= -3.0544$; $d.f.=39$; $p<.005$). Each of the four subgroups reflected this increase (see TABLE 14A), although in only the two

SIZE OF WRITING

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 4.4725 | 1.6686 | 5.0150 | 1.8781 | 19 | -2.2178** |
| PE | 4.8956 | 1.6578 | 5.6611 | 1.3870 | 8 | -2.1429** |
| PA+OP | 3.7600 | 0.9607 | 4.1000 | 0.8718 | 4 | -1.2981 |
| PE+OP | 2.6333 | 0.9201 | 3.0833 | 1.3801 | 5 | -1.2529 |
| GROUP | 4.2027 | 1.6357 | 4.7562 | 1.7732 | 39 | -3.0544** |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 1.0793 | 1 | 1.0793 | 0.4692 |
| SURGERY | 16.9604 | 1 | 16.9604 | 7.3729* |
| INTERACTION | 3.4932 | 1 | 3.4932 | 1.5185 |
| ERROR | 82.8135 | 35 | 2.3004 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.3823 | 1 | 0.3823 | 0.1449 |
| SURGERY | 22.2429 | 1 | 22.2429 | 8.4317** |
| INTERACTION | 5.0276 | 1 | 5.0276 | 1.9058 |
| ERROR | 94.9683 | 36 | 2.6380 | |

D. ANALYSIS OF COVARIANCE

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.0688 | 1 | 0.0688 | 0.0682 |
| SURGERY | 1.2353 | 1 | 1.2353 | 1.2255 |
| INTERACTION | 0.4339 | 1 | 0.4339 | 0.4304 |
| ERROR | 35.2801 | 35 | 1.0080 | |

TABLE 14

larger subgroups did the change reach at least the .05 per cent level of significance. (*PA*: t= -2.2178; d.f.=19; p<.025 *and PE*: t= -2.1429; d.f.=8; p<.05).

Analysis of variance of the after treatment measures showed that there was no significant difference between the size of writing of paralysis agitans patients and post-encephalitic patients. A significant difference, however, was found between patients who had undergone surgery and those who had not. (See TABLE 14C). Operated patients wrote smaller words than did unoperated patients.

Since both before and after treatment it was found that operated patients wrote smaller than unoperated patients a difficulty in interpretation of the results arises. Do the patients, irrespective of surgical history, respond comparably to treatment? In other words is the after treatment difference in the size of writing merely a reflection of the before treatment difference or "bias" in performance? Or, does a surgical history limit the degree of improvement? Is the difference in size of writing after treatment a reflection of different degrees of response to treatment? Do unoperated patients (who happen to write larger) improve more or, indeed, less than do operated patients (who happen to write smaller)?

To resolve this difficulty, the data was reanalysed using an analysis of covariance in which the after treatment data was adjusted in terms of the before treatment data. As can be seen from TABLE 14D which

contains the results of this analysis, when the adjustment is made no differences of significance are found either between the two types of Parkinsonism studied, or, more pertinently, between the patients who had and those who had not previously undergone subcortical surgery. These results quite clearly reveal comparable degrees of increase in the size of writing amongst the patients, irrespective of surgical history, and of type of Parkinsonism.

TIME TAKEN TO WRITE

Before treatment the group took, on average, 40.38± 16.83 seconds to write their names and addresses. The mean writing times for the four subgroups are contained in TABLE 15A. Analysis of variance of these before treatment measures revealed significant differences between patients who had and those who had not undergone surgery ($F=5.9619$; $d.f.=1,30$; $p<.05$). The patients who had not undergone surgery took less time to write their names and addresses than the patients who had. Type of Parkinsonism, however, was not found to be a significant factor (see TABLE 15B).

After treatment, the group took on average 35.04± 12.42 seconds to write their names and addresses. The mean writing times for the four subgroups are contained in TABLE 15A. Although inspection of this table reveals an after treatment reduction in both mean times and standard deviations for the group as a whole and for the four

TIME TAKEN TO WRITE

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 36.9724 | 16.2789 | 31.9774 | 12.5287 | 15 | 0.9818 |
| PE | 34.1700 | 9.6064 | 29.9237 | 7.2851 | 7 | 1.3937 |
| PA+OP | 49.1720 | 20.9452 | 40.6600 | 10.7071 | 4 | 1.6888 |
| PE+OP | 52.4340 | 18.4892 | 47.3980 | 12.5293 | 4 | 1.0822 |
| GROUP | 40.3808 | 16.8330 | 35.0388 | 12.4238 | 33 | 1.9190 |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 13.9570 | 1 | 13.9570 | 0.0541 |
| SURGERY | 1538.8203 | 1 | 1538.8203 | 5.9619* |
| INTERACTION | 54.5352 | 1 | 54.5352 | 0.2113 |
| ERROR | 7743.2656 | 30 | 258.1086 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 54.3125 | 1 | 54.3125 | 0.4274 |
| SURGERY | 1145.0391 | 1 | 1145.0391 | 9.0100** |
| INTERACTION | 81.6992 | 1 | 81.6992 | 0.6429 |
| ERROR | 3812.5508 | 30 | 127.0850 | |

D. ANALYSIS OF COVARIANCE

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 41.3186 | 1 | 41.3186 | 0.3603 |
| SURGERY | 480.6089 | 1 | 480.6089 | 4.1909* |
| INTERACTION | 55.7153 | 1 | 55.7153 | 0.4858 |
| ERROR | 3325.6980 | 29 | 114.6792 | |

TABLE 15

subgroups, none of the t-tests comparing before and after treatment measures reached significance. The time taken to write the same sample did not change with dopamine replacement and the consequent reduction of akinesia.

Not surprisingly, therefore, analysis of variance of the after treatment writing times provided a picture very similar to that found before treatment. As can be seen from the tabulation of results in TABLE 15C, type of Parkinsonism was once again found not to be a significant factor, while surgical history was again found to be a significant factor. Operated patients wrote far slower than unoperated patients.

These results are interesting, particularly in the context of the ascertained increase in size of writing with treatment. Clearly there is evidence of writing more rapidly after treatment: the patients wrote substantially larger words after treatment in about the same time as it had taken them to write micrographically before treatment. Furthermore, there is clear indication that stereotactic subcortical surgery had an adverse and lasting effect on a highly-practiced complex motor activity such as writing. Although surgery did not limit the degree of improvement with dopamine replacement, both before and after treatment operated patients wrote smaller and slower than their unoperated counterparts.

# SUMMARY

The group of patients selected for the present study were predominantly akinetic. Although all four subgroups were found to have 'severe' akinesia, analysis of the clinical ratings revealed that patients with a surgical history were more profoundly akinetic than patients who had not undergone subcortical stereotactic surgery. No difference in degree of akinesia was found between paralysis agitans and post-encephalitic Parkinsonian patients.

The group as a whole was found to have only 'slight' tremor and 'moderate' rigidity. The degree of these 'positive' symptoms varied significantly neither with surgical history nor with type of Parkinsonism.

The question of the efficacy of surgery in reducing positive symptoms was considered. It was found that when length of illness before surgery and length of illness when this investigation commenced are taken into account, efficacy of surgery is found to vary with type of Parkinsonism.

Ratings of clinical improvement with L-dopa treatment showed that although all patients made at least some improvement, paralysis agitans patients showed significantly more improvement than post-encephalitic Parkinsonian patients. Clinical improvement did not vary with surgical history: no difference was found in degree of clinical improvement between operated and unoperated

patients.

Findings from measures of the size of writing and time spent writing showed that both size and time of writing varied significantly with surgical history. Both before and after treatment it was found that unoperated patients wrote larger words and spent less time writing these larger words than operated patients. With treatment all patients showed an increase in size of writing and a decrease in writing time. However, not all patients showed the same amount of improvement. Unoperated patients were found to have made significantly greater improvement on both these tasks with treatment than did operated patients.

The latency for writing on command both before and after treatment varied significantly with type of Parkinsonism. Paralysis agitans patients were faster than post-encephalitic Parkinsonian patients. On comparing before and after treatment latencies it was found that the group as a whole was significantly faster after treatment. Not all subgroups reflected this increase however. Only unoperated patients improved with treatment. Analysis of covariance confirmed that reduction in response latency varied significantly with surgical history. Type of Parkinsonism did not appear to limit the degree of improvement on this task.

# CHAPTER 7

## RESULTS II: EVALUATION OF SPEECH DISTURBANCE IN PATIENTS WITH LESIONS OF THE BASAL GANGLIA

Previous workers in the field of Parkinsonian dysarthria have for the most part ignored the role of akinesia. It was therefore necessary to proceed aprioristically in order to arrive at basic information essential to the rest of the investigation. Fundamental questions were asked: What is the prevalence, severity and nature of the speech disturbance in a group of predominantly akinetic Parkinsonian patients? Is the disturbance in speech related to the degree of subcortical damage? Is this speech disturbance modified by the reduction in akinesia consequent upon administration of L-dopa?

Answering questions such as these involves making normative judgements. Speech samples of forty-three Parkinsonian patients were recorded on magnetic tape (see Chapter 5) before treatment with L-dopa had commenced

('test') and again ('retest') once the neurologist in charge was satisfied that each patient was on his own maximal dosage level of L-dopa and was showing clinical improvement in general motor ability. The forty-three patients comprised twenty paralysis agitans patients with no history of subcortical surgery (subgroup PA); eight paralysis agitans patients with a history of subcortical surgery (subgroup PA+OP); nine post-encephalitic Parkinsonian patients without a relevant surgical history (subgoup PE) and six with such a history (subgroup PE+OP). The eighty-six recorded speech samples were played to two judges experienced in evaluating disordered speech. The judges were asked to direct their attention to five parameters of speech, defined for this study by the rating-scales. They were required to decide, for each speech sample, whether there was disturbance on any of these parameters and, if so, to rate the severity of this disturbance on a five-point scale. (Maximum severity was 5). The scales were: INTELLIGIBILITY, DYSARTHRIA, PROSODY, FESTINATION and PHONIC. The construction of the scales, the procedure followed in obtaining the judges' evaluations and the reliability as between the judges' ratings have been discussed in Chapter 5.

## METHODS OF ANALYSIS

The two sets of data (i.e. the before treatment or

'test' data and the after treatment or 'retest' date) were non-parametric in nature and were subjected to similar methods of analysis. Basically two different sets of analysis of variance tests were used. In the first set of analyses each of the five rating-scales was considered independently. The Kruskal-Wallis test was employed to ascertain whether, on each scale, the severity of impairment varied across the four subgroups. Where necessary, comparisons between individual subgroups were carried out using Mann Whitney tests. In the second set of analyses each subgroup's degree of impairment on all five scales was considered. Friedman's analysis was used to test (for each subgroup) the variance of severity of impairment across the five scales. This was followed up by calculating and testing the concordance amongst the rating scores of sub-group members. Kendall (1948) has suggested that when there is significant concordance the ranked entities (in this case the rating-scales) may be ordered in terms of their respective sums of the pooled-ordered scores. The rating-scales may thus be considered in terms of their contribution to the total pattern of impairment for each subgroup. By this method, therefore, it is possible to see whether patterns of impairment differ according to type of Parkinsonism and/or surgical history.

To see whether L-dopa treatment had any effect on speech, the differences between test and retest ratings were tested by means of Wilcoxon's matched-pairs signed-

ranks tests. In three cases where $n$ was too small for the test to be valid, the binomial test was used.

Where appropriate, one-tailed tests were used. The hypothesis underlying all these tests was: The greater the neurological damage, the greater the speech disturbance. Thus the following distribution of disturbance was predicted: PA<PE; PA+OP<PE+OP and PA<PA +OP; PE<PE+OP. Moreover, if the hypothesis that Parkinsonism is a dopa-deficiency syndrome is correct, it would follow that test > retest.

## SPEECH DISTURBANCE BEFORE TREATMENT HAD COMMENCED

### INCIDENCE OF SPEECH DISTURBANCE

#### INTELLIGIBILITY

Three patients (7%) out of the total group of forty-three were found to have no impairment at all on the scale INTELLIGIBILITY. A further three patients (7%) were considered by the judges to have perceptible, yet minimal, disturbances (within normal limits, i.e. being given an average of 0.5 points by the judges). Thus only 14% of the patient group had speech that the judges considered acceptable, and 86% had some impairment in intelligibility. As FIGURE 18A illustrates, the impairment scores for these patients ranged from 1 to 4.5, are negatively skewed with a mode of 4.0. The median for the total group of forty-three patients was 2.66.

DISTRIBUTION OF RATINGS BEFORE TREATMENT

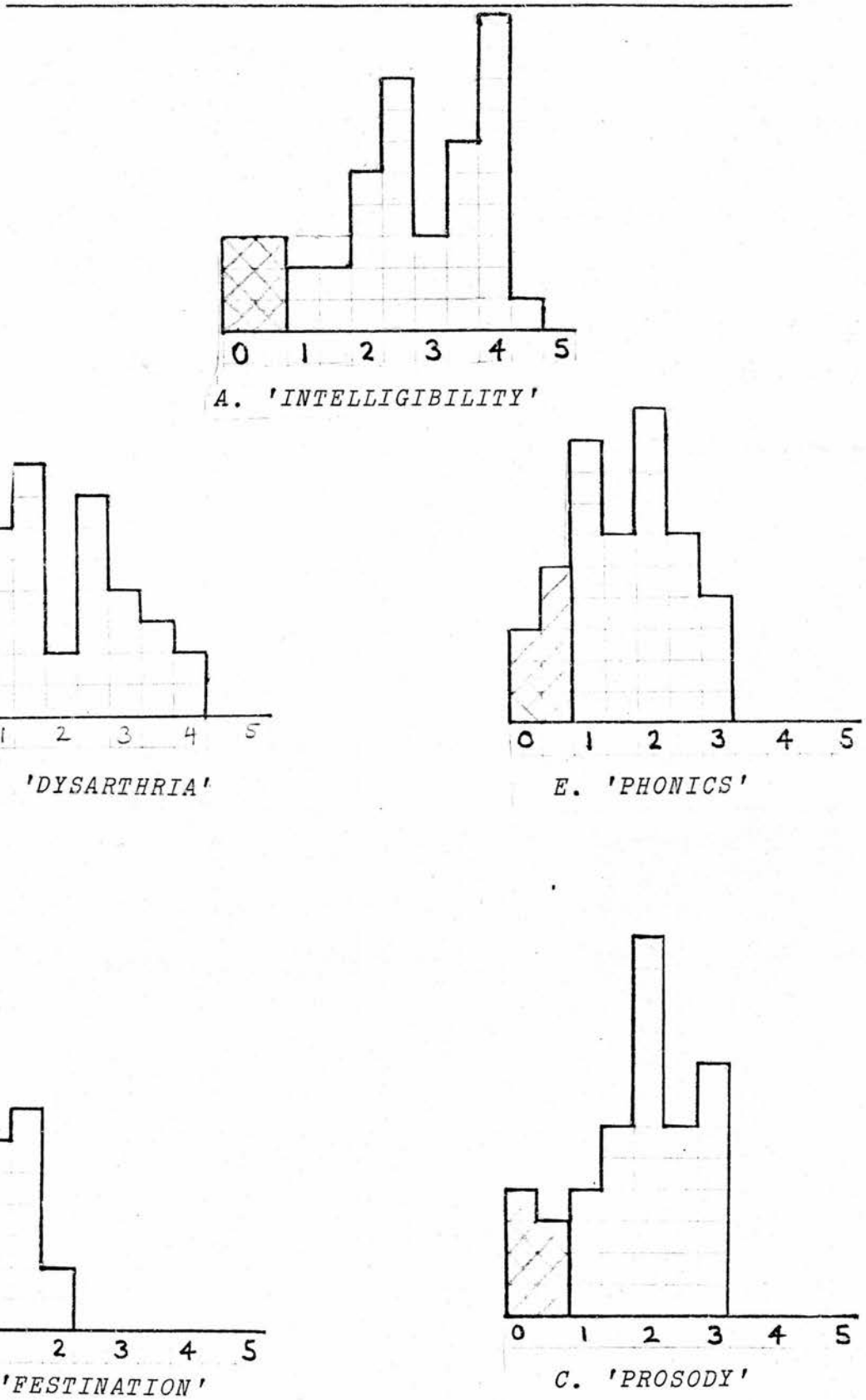



FIGURE 18

DYSARTHRIA:

Just over a quarter of the total patient group (26%) were found to have articulation of speech within 'normal' limits. Of these, 14% were without any dysarthria, and a further 12% had preceptible, yet minimal articulatory disturbance. The remaining 74% of the group had dysarthria of varying degrees. The rating-scores given these patients ranged from 1 ('mild') to 4 ('moderate-to-severe'), were positively skewed in distribution with a mode of 1.5. (See FIGURE 18B). The median for the whole group was 1.53.

PROSODY:

Only 9% of the forty-three patients had no disturbance at all in prosodic features. A further 7% had perceptible but minimal disturbance. Thus only 16% of the group were considered to have adequate or 'normal' speech on this scale, and 84% to have some disturbance. As can be seen from FIGURE 18C, the degree of disturbance of ratings was skewed marginally to the left with a mode at 2.0. The median for the group as a whole was 1.94.

FESTINATION:

In marked contrast to the other disturbances, festination was seen in only approximately one third of the forty-three patients. Moreover, even among the 35% affected, it was not a particularly marked disturbance. Festination was rated between 1 ('mild') and 2 ('mild

to moderate'). The distribution of scores is positively skewed, with the mode at 1.0 (See FIGURE 18D). The median for the group as a whole was 0.5.

PHONIC:

Of forty-three patients 19% were considered to have speech within normal limits on this parameter, This segment of the group comprised 7% with no disturbance at all, and a further 12% with perceptible yet minimal impairment. The 81% of patients who were considered impaired on this rating-scale were found to have 'slight' (1) to 'moderate' (3) impairment (See FIGURE 18E). The distribution of impairment scores is skewed positively, with a mode of 2.0. The median for the group as a whole was 1.63.

DEGREE OF SPEECH IMPAIRMENT

The degree of impairment on the scale INTELLIGIBILITY varied significantly with patient group ($H=8.830, d.f.=3, p<.05$). Patients with paralysis agitans who had no history of subcortical surgery were significantly more intelligible than paralysis agitans patients who had previously undergone subcortical surgery ($U=37.0, p=.025$) and post-encephalitic patients with no surgical history ($U=45.5, p<.025$). No significant difference was found between the two postencephalitic groups, nor between the two groups who had undergone surgery. Clearly, Parkinsonism of encephalitic origin and/or previous

surgical history is associated with greater impairment in intelligibility.

The degree of dysarthria varied significantly with patient subgroup (H=11.0710, d.f.=3, p<.01>.001). Subgroup PA had significantly less dysarthria than subgroup PA+OP (U=30.5, p<.01>.001), and subgroup PE (U=48.5, p<.05>.025).

No significant variation in degree of impairment between subgroups was found on the other scales, PROSODY, FESTINATION and PHONIC. See TABLE 16.

ANALYSIS OF VARIANCE[1] OF DEGREE OF SPEECH IMPAIRMENT BEFORE TREATMENT AMONGST THE FOUR SUB-GROUPS

| RATING SCALE | H | D.F. | p |
|---|---|---|---|
| INTELLIGIBILITY | 8.8830 | 3 | <.05>.02 |
| DYSARTHRIA | 11.0710 | 3 | <.02>.01 |
| PROSODY | 5.6800 | 3 | >.05 |
| FESTINATION | 7.0123 | 3 | >.05 |
| PHONICS | 4.0220 | 3 | >.05 |

[1] *Kruskal-Wallis analysis of variance*

TABLE 16

PATTERNS OF SPEECH IMPAIRMENT

A significant variation in degree of impairment across the five scales was found within the group as a whole and within the four subgroups (See TABLE 17A). There was, in addition, significant concordance between group-members and between subgroup-members in their ratings on the five scales. (See TABLE 17B).

Kendall (1948) has suggested that when there is significant concordance amongst several sets of rankings,

'PATTERNS' OF SPEECH BEFORE TREATMENT

A. ANALYSIS OF VARIANCE[1] OF DEGREE OF DISTURBANCE ACROSS FIVE RATING-SCALES

| SOURCE | d.f. | $Xr^2$ | p |
|---|---|---|---|
| PA | 4 | 32.6800 | <.001 |
| PE | 4 | 22.7556 | <.001 |
| PA+OP | 4 | 22.8000 | <.001 |
| PE+OP | 4 | 17.4333 | <.01 |
| GROUP AS A WHOLE | 4 | 84.9814 | <.001 |

[1] *Friedman's*

B. DEGREE OF CONCORDANCE AMONGST SUB-GROUP MEMBERS

| SOURCE | k | W | p |
|---|---|---|---|
| PA | 20 | 0.4085 | <.01 |
| PE | 9 | 0.6321 | <.01 |
| PA+OP | 8 | 0.7125 | <.01 |
| PE+OP | 6 | 0.7264 | <.01 |
| GROUP AS A WHOLE | 43 | 0.4941 | <.001 |

TABLE 17

the ranked entities (in this case the rating-scales) may be ordered scores. Ranking the scales in this way succinctly indicates the relative 'weight' or predominance of each scale in the total pattern of speech impairment. In descending order of predominance, the scales rank as follows:

For the group as a whole:
INTELLIGIBILITY, PROSODY, DYSARTHRIA, PHONIC, FESTINATION.

For subgroup PA:
INTELLIGIBILITY, PROSODY, PHONIC, DYSARTHRIA, FESTINATION.

For subgroup PA+OP:
INTELLIGIBILITY, DYSARTHRIA, PROSODY, PHONIC, FESTINATION.

For subgroup PE:
INTELLIGIBILITY, DYSARTHRIA, PROSODY, PHONIC, FESTINATION.

For subgroup PE+OP:
INTELLIGIBILITY, DYSARTHRIA, PROSODY, PHONIC, FESTINATION.

The patterns are similar in a number of respects: in all cases INTELLIGIBILITY is at the top of the list, FESTINATION at the bottom, and PROSODY always preceeds PHONIC. The difference in patterns is attributable solely to the position of DYSARTHRIA in the rankings. In subgroup PA, DYSARTHRIA is penultimate while for the other sub-groups it is second. This is not totally unexpected. In the preceeding section, it was shown that there was a significant variation in the degree of DYSARTHRIA across the four subgroups. PA was significantly less dysarthric than the other subgroups and these other subgroups were equally disturbed in articulation.

However, similar significant variations were found on the scale INTELLIGIBILITY. PA was significantly more intelligible than the other subgroups, while these subgroups, PA+OP, PE, PE+OP, did not differ amongst themselves in the degree of impairment in intelligibility. One could argue that despite this significant variation across the subgroups, since INTELLIGIBILITY is consistently the scale showing the most impairment, it is a global or super-ordinate scale reflecting the composite

disturbances of the four more 'specific' scales. The argument could be extended to exclude INTELLIGIBILITY from the ranking lists altogether. Indeed, on omitting this scale and re-analysing the data from only the 'specific' scales, precisely the same ordering of scales is obtained for the group as a whole and for the four subgroups.

The pattern of 'PROSODY, PHONIC, DYSARTHRIA, FESTINATION' that was obtained for paralysis agitans patients who have no previous surgical history is in keeping with the study by Darley et al. (1969a, 1969b). In that study, three judges were able to differentiate patterns of dysarthria associated with a variety of neurological diseases. Parkinsonian patients constituted one of the groups of patients involved in this study. The parameters the judges found most useful in distinguishing Parkinsonian speech from the other types of speech disorder were those relating to prosodic features - "MONOPITCH" (defined as lacking in "normal pitch and inflectional changes"); "REDUCED STRESS" (reduction of "proper stress or emphasis patterns"); and "MONOLOUDNESS" (lack of "normal variations in loudness"). The next most useful parameter was "IMPRECISE ARTICULATION OF CONSONANTS". This was followed by three parameters relating to speed of utterance: "INAPPROPRIATE SILENCES", "SHORT RUSHES" (of speech): and "VARIABLE RATE" ("festination").

The relative predominance of dysarthria in the other sub-groups is not totally unexpected. Cramer (1940)

emphasised the role of dysarthria in the pattern of speech impairment in the six post-encephalitic patients she studied and the effect of stereotactic surgery on the speech of "Parkinsonian" patients, according to Allen et al. (1966), Herman et al. (1966), and Bell (1968) is to increase dysarthria. What is surprising, is that no significant difference in the degree of dysarthria was found amongst these three groups. One would have predicted that since paralysis agitans patients who have undergone surgery have (in comparison to unoperated paralysis agitans patients) an overlay of dysarthria, the same would hold true of post-encephalitic patients. Those post-encephalitic patients with a surgical history might be expected to have more severe and marked dysarthria than those with no surgical history. This, however, was not found to be the case.

## SPEECH DISTURBANCE AFTER TREATMENT HAD COMMENCED

### INCIDENCE OF SPEECH IMPAIRMENT

After treatment, a larger proportion of the patients in the study were considered by the judges to have speech within 'normal' limits.

#### INTELLIGIBILITY:

After L-dopa treatment had been stabilized in each patient, 23% of the group, a proportion 9% larger than on previous testing, were found to have speech within

'normal' limits. This group comprised 9% who were without any impairment at all, and 14% with perceptible, yet minimal, impairment. The scores of the remaining 77% of the group (who had impairment of intelligibility) although of a slightly larger range than previously, were no longer negatively skewed in distribution. As FIGURE 19A illustrates, the distribution of impairment-scores assumes a shape closer to a normal distribution. This is reflected in the values of the mode (2.75) and the median (2.46) of these scores.

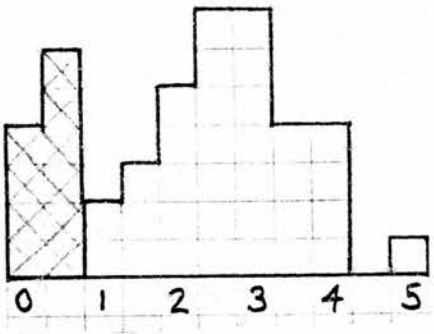
DYSARTHRIA:

On retest, 37% of the patients were found to have either minimal or no dysarthria. This was an improvement of 11%. The 63% of patients with dysarthria had scores ranging from 1 ('mild') to 5 ('severe') with a mode of 2 and a median of 1.38. The distribution of scores (See FIGURE 19B) was positively skewed.

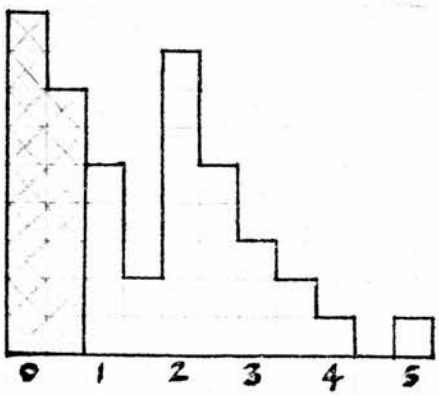
PROSODY:

On retest, after L-dopa treatment had commenced, 7% more of the patients had speech with 'normal' prosodic features than on first testing. The 23% of the group with 'normal' prosody comprised 7% with no disturbance at all, and 16% with perceptible yet minimal disturbance. Disturbance in prosodic features was found in 77% of the group. The severity of disturbance was found to range from 1 ('slight') to 3 ('moderate'). The distribution of impairment-ratings was negatively skewed, with a mode of 2.5, and a median of 1.63. See FIGURE 19C.

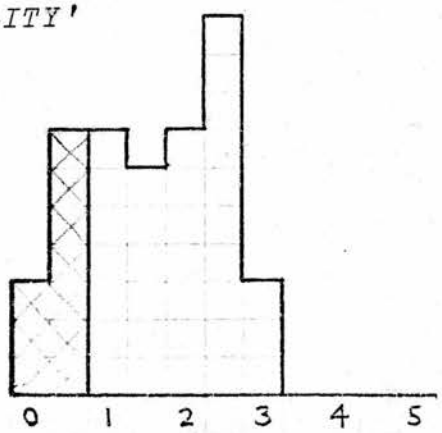
DISTRIBUTION OF RATINGS AFTER TREATMENT



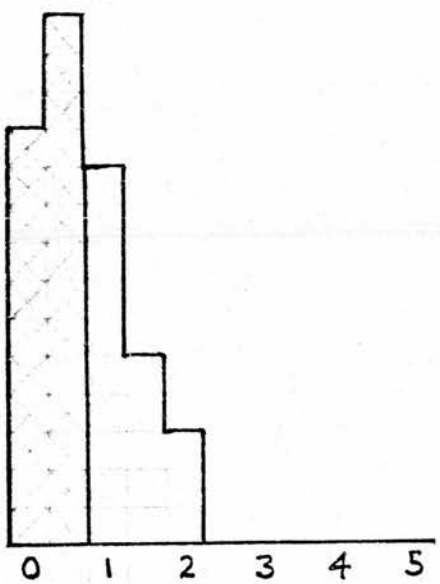

A. 'INTELLIGIBILITY'



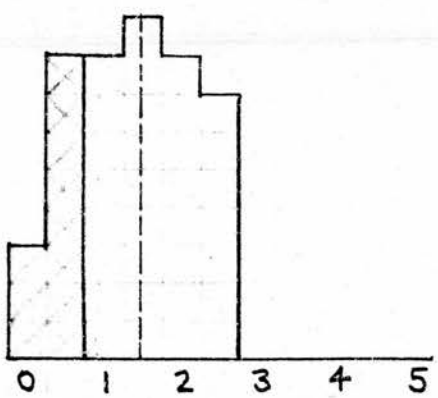

B. 'DYSARTHRIA'




C. 'PROSODY'




D. 'FESTINATION'




E. 'PHONICS'

FIGURE 19

FESTINATION:

On retest, a slight increase in the number of patients with festinant speech was found. Whereas before treatment 35% of patients had festination, on retest 41% were rated as disturbed on this parameter. (As will be shown later, this anomaly is largely attributable to one group viz. PE+OP.) The degree of disturbance, however, was over the same range as before treatment, from 1 ('mild') to 2 ('mild to moderate'). The mode of these disturbance ratings was 1.0 and the median 0.63. See FIGURE 19D.

PHONIC:

An increased proportion of patients were considered to have speech within normal limits, on this rating-scale, after treatment. As can be seen from TABLE 1.5, on retest 7% more patients were found to have a perceptible yet minimal disturbance than on first testing. On retest, the range of disturbance-ratings was found to be smaller (See FIGURE 19E). The mode of disturbance-ratings was 1.5, and the median 1.39.

DEGREE OF SPEECH IMPAIRMENT

INTELLIGIBILITY:

The degree of impairment varied significantly with patient group ($H=23.0706$, $d.f.=3$, $p<.001$). Unoperated patient groups were significantly more intelligibile than their operated counterparts (*PA<PA+OP*:$U=10$, $p<.001$;

*PE<PE+OP:* U=11, p<.05>.025). Furthermore, the two unoperated groups were significantly different; subgroup PA was more intelligible than subgroup PE (U=53, p<.05 >.025). No difference of significance was found between the two patient subgroups with previous surgical history.

DYSARTHRIA:

The degree of dysarthria varied significantly with patient subgroup (H=18.8830, d.f.=3, p<.001). Patients with no previous surgical history were significantly less dysarthric than their operated counterparts (*PA<PA+OP:* U=11.5, p<001; *PE<PE+OP:* U=11, p<.05). Paralysis agitans patients without surgical history had markedly less dysarthria than post-encephalitic patients without surgical history (U=53, p<.05>.025). However, paralysis agitans patients who had a history of subcortical surgery were not less dysarthric than post-encephalitic patients with a history of subcortical surgery.

PROSODY:

Analysis of retest scores showed that the degree of impairment varied significantly with patient group (H=14.1041, d.f.=3, p<.001). Patients without previous surgical history had significantly less prosodic disturbance than their operated counterparts (*PA<PA+OP:* U=22.0, p<.01>.001; *PE<PE+OP:* z=1.9331, p<.0268). No significant difference was found between the two forms of Parkinsonism in this study, neither between the groups without a history of previous surgery (PA,PE),

nor between those groups which had previously undergone surgery (PA+OP, PE+OP).

FESTINATION:

A significant variation in degree of impairment on this scale was found according to patient subgroup ($H=9.7213$, d.f.=3, $p<.05>.02$). Unoperated paralysis agitans patients had significantly less festination than operated paralysis agitans patients ($U=25$, $p<.01>.001$). The difference between unoperated and operated post-encephalitic patients just failed to reach significance (*PE<PE+OP*: $z=1.555$, $p=.0594$). No difference was found between subgroups PA and PE, or subgroups PA+OP and PE+OP.

PHONIC:

The degree of disturbance varied significantly with patient subgroup ($H=14.2958$, d.f.=3, $p<.01>.001$). Patients who had no history of surgery, irrespective of type of Parkinsonism, were significantly less impaired on this rating-scale on retest than those who had previously undergone surgery (*PA<PA+OP*: $U=33.5$, $p<.01>.001$; *PE<PE+OP*: $U=6.5$, $p<.01>.001$).

CHANGES IN SPEECH DISTURBANCE: test-retest comparisons

INTELLIGIBILITY:

The group as a whole was significantly more intelligible after treatment ($T=31$, $n=24$, $p<.005$). The two unoperated subgroups were found to have improved

significantly (*PA*: T=0, n=10, p<.001; *PE*: (on binomial test), x=0, n=5, p=.031) but the two subgroups with a previous surgical history showed no significant change.

DYSARTHRIA:

The group as a whole was found to be significantly less dysarthric after treatment had begun (z=1.6366, p<.05). Both subgroups without surgical history showed a significant improvement (*PA*: T=10, n=11, p<.025>.01; *PE*: T=0, n=7, p<.01>.001). The two other subgroups, PA+OP and PE+OP, showed no significant change.

PROSODY:

A significant reduction in disturbance of prosodic features was found for the group as a whole after treatment had begun (z=2.0048, p<.023>.022). However, only one subgroup, subgroup PA, showed a significant improvement on this scale (T=8, n=13, p<.003).

FESTINATION:

No significant change was found for the group as a whole on this scale. However, when considering the subgroups individually, a significant change was found in one of the subgroups. Subgroup PE+OP was significantly more impaired on this scale after treatment (x=0, n=5, p=.031).

PHONIC:

The group as a whole showed a significant improvement on this scale after treatment had commenced (T=81, n=25, p<.025>.01). Of the four subgroups, however only

subgroups PA and PE showed significant reduction in phonic disturbances (*PA*: T=12, n=12, $p<.025>.01$; *PE*: (binomial test) x=0, n=5, p=.031). The two subgroups with previous surgical history did not change significantly.

These findings are clearly in direct contrariety to the editorial comments: on the limitations in treatment of Parkinson's disease made by Schwab (1968): "Still further future hopes are needed to help cases with difficulty in speech and handwriting that many patients have At present... L-dopa can not do very much for either." However, the improvement in speech with L-dopa treatment reported herein is in clear accordance with the two studies published after this investigation had begun. Rigrodsky and Morrison (1970) compared the speech performances before and after L-dopa treatment of a group of twenty-one Parkinsonian patients. On only one of the four rating-scales used was a significant change found ($\alpha=.05$). This scale, the "time factor in speaking", was a measure of the "overall rate of speaking, the appropriateness of phrasing and pauses, the rhythm and fluency of speech". The three other scales ("overall adequacy", "clarity of articulation", and "nasal resonance"), however, did reveal a "trend in the direction of improved speech during L-dopa therapy". Nakano et al. (1973), in a double-blind crossover study, found that when their eighteen patients "with Parkinson's syndrome" were on L-dopa (as opposed to a

placebo or procyclidine hydrochloride) the "intelligibity" of their speech was much improved. They believed this improvement to be attributable to the "improvement in the articulation" of their patients.

## PATTERNS OF SPEECH IMPAIRMENT

After treatment, despite the significant reduction in impairment seen for the group as a whole (on all scales except FESTINATION) a significant degree of variation across the rating-scales was found. When the scales are ranked in terms of their relative contribution to the overall picture of impairment, FESTINATION - the one scale on which no improvement (or deterioration) was observed - remained the least predominant disturbance. The order of scales, from most to least predominant is: (INTELLIGIBILITY), PROSODY, PHONIC, DYSARTHRIA, FESTINATION. It appears that L-dopa treatment affects speech impairment in two ways: it reduces the severity of impairment in terms of intelligibility, articulation, prosodic features and vocal quality; and it alters the overall pattern of disturbance. After L-dopa treatment, dysarthria is a less predominant feature.

For all the four subgroups, degree of impairment varied across the five scales (See TABLE 18A). There was also a significant degree of concord within each group (See TABLE 18B). The four subgroups, however, were not all affected similarly by L-dopa.

Subgroup PA appears to have been affected only in

A. ANALYSIS OF VARIANCE[1] OF DEGREE OF DISTURBANCE ACROSS FIVE RATING-SCALES

| SOURCE | d.f. | $Xr^2$ | p |
|---|---|---|---|
| PA | 4 | 20.1700 | <.001 |
| PE | 4 | 14.1111 | <.01 |
| PA+OP | 4 | 19.3250 | <.001 |
| PE+OP | 4 | 18.0000 | <.01 |
| GROUP AS A WHOLE | 4 | 114.3116 | <.001 |

[1] *Friedman's*

B. DEGREE OF CONCORDANCE AMONGST SUB-GROUP MEMBERS

| SOURCE | K | W | p |
|---|---|---|---|
| PA | 20 | 0.2521 | <.01 |
| PE | 9 | 0.4083 | <.01 |
| PA+OP | 8 | 0.6039 | <.01 |
| PE+OP | 6 | 0.7500 | <.01 |
| GROUP AS A WHOLE | 43 | 0.3251 | <.001 |

TABLE 18

terms of a reduction in quantity of disturbance. The quality was unaffected: the relative amounts each scale contributed to the overall pattern of impairment is almost identical before and after treatment despite significant reductions in degree of disturbance on all scales except FESTINATION.

In subgroup PE, however, treatment affected both the quantity and quality of speech impairment. After

treatment the relative amounts each scale contributed to the overall pattern of impairment differed from those before treatment. After treatment, in order of predominance, the scales rank as follows: (INTELLIGIBILITY), PROSODY, DYSARTHRIA, PHONIC, FESTINATION. Some change could, perhaps, have been expected since this subgroup improved on INTELLIGIBILITY, DYSARTHRIA and PHONIC but remained unaffected on PROSODY and FESTINATION. However, what is particularly interesting is the way in which the scales are ordered after treatment. PROSODY and not DYSARTHRIA is now the predominant disturbance. In this respect subgroup PE resembles subgroup PA more closely than the operated counterpart PE+OP. This closer affinity to the other unoperated Parkinsonian group, and the widening of differences from operated post-encephalitic patients is in accordance with the changes in degree of disturbance already discussed.

Patients who had previously undergone surgery remained largely unaffected by treatment. DYSARTHRIA was still the predominant disturbance, and even though post-encephalitic patients with a surgical history increased in their amount and degree of festination, the order in which the scales contribute to the overall pattern of impairment is identical to that found before treatment.

# SUMMARY

Before treatment, predominantly akinetic Parkinsonian patients have a high incidence of speech disturbance. Over 80% have reduced intelligibility, disturbances of prosody and of phonic quality. Furthermore, over 70% are dysarthric. Festination, however, was not found to be a marked disturbance - only one out of every three patients exhibited this temporal distortion.

The degree of impairment on INTELLIGIBILITY and DYSARTHRIA before treatment varied significantly between the four subgroups. In each case unoperated paralysis agitans patients were less impaired than the three other subgroups.

Some variation between the subgroups was observed in the relative importance of the five parameters. Before treatment paralysis agitans patients without previous surgical history were predominantly a-prosodic while the three other subgroups were predominantly dysarthric.

After treatment, the intensity of disturbance on each of the five parameters varied significantly between the subgroups. Unoperated patient subgroups were generally less impaired than their operated counterparts; and on INTELLIGIBILITY and DYSARTHRIA PA proved less impaired than PE.

Within subgroup PE a notable change in the nature of speech disturbance was observed. Whereas before treatment the speech of this subgroup was undifferentiable from the

two subgroups with surgical history, after treatment the speech of subgroup PE resembled more closely that of subgroup PA. After treatment, the speech of the two unoperated subgroups was characterized by a relative predominance of prosodic disturbances and that of the operated groups by dysarthric disturbances.

Test-retest comparison showed that for the group as a whole, there was significant improvement on four of the five scales. The only scale on which no reduction (and indeed, no increase) was demonstrated was FESTINATION. Of the four subgroups, PA showed a significant reduction in disturbance on all five parameters. Subgroup PE showed a significant improvement on all scales except PROSODY and FESTINATION. The two other subgroups, however, fared less well. Of these two subgroups with a history of subcortical surgery, only PE+OP showed any significant change. Unfortunately this change (on FESTINATION) was for the worse.

# CHAPTER 8

## RESULTS III: THE DESCRIPTION OF SPEECH

The speech samples that had been played to the judges for evaluation were also subjected to analysis in an attempt to obtain parametric, 'objective' measures characteristic of the samples. A number of standard measures were taken such as rate of reading and voice volume. In addition, the samples were subjected to certain novel methods of analysis. The purpose of these was to investigate the fine temporal changes in speech that occur with Parkinsonism and that are possibly reversed by dopamine replacement therapy. These analyses provided quantification of the periodicity of words and pauses, and of the regularity of speech.

The results will be presented in two sections. The first, *Vocal Characteristics*, covers mean voice volume, variation in voice volume, and sustained phonation. The second section, *Temporal Characteristics*, covers rate of reading, the length of phonations, and pauses and the regularity of speech.

## METHODS OF ANALYSIS

The results presented in this chapter are from parametric tests based on interval data. The choice of statistical techniques was governed by the two basic experimental hypotheses.

The first hypothesis related the degree of subcortical damage to the degree of speech disturbance and predicted that the larger the extent of the lesion/s the greater would be the speech disturbance. The differences before treatment in degree of disturbance between the four subgroups (each of which represented a different degree of subcortical damage) were tested using an analysis of variance with two fixed factors - type of Parkinsonism and surgery. The same ANOVA was used on the after treatment scores unless significant differences were found in the before treatment scores, in which case an analysis of covariance with the same two factors was used. The effect of this technique was to 'adjust' each after treatment score in terms of the before treatment score. Where appropriate, inter-subgroup comparisons were made using the t-test (for individual samples).

The second hypothesis proposed a connection between the speech disturbance and the dopamine concentration levels of the striatum. It was hypothesised that dopamine replacement would be reflected in a diminution of speech disturbances. To test this hypothesis, one-tailed t-tests for 'paired samples' were used, with each patient acting as his own control.

# VOCAL CHARACTERISTICS

## VOICE VOLUME

Voice volume measures were based on the recordings of the patients reading the standard passage "Arthur the Rat". Measures were taken at five second intervals throughout the reading (see Chapter 5). For each patient, both before and after treatment, the means and variances of these measures were calculated and subjected to statistical analysis.

### MEAN VOICE VOLUME

Before treatment the group of patients was found to have an average voice volume level of 63.3± 6.26 dB. Subgroup PE+OP spoke the softest (60.02± 4.32 dB) and subgroup PE the loudest (64.39± 6.05 dB). (see TABLE 19A). Analysis of variance revealed no significant differences between the subgroups: neither type of Parkinsonism nor surgical history was of importance as far as voice volume levels were concerned. (see TABLE 19B).

The finding that operated patients spoke no softer than unoperated patients is particularly interesting. In 1966 two studies of the effect of surgery on voice volume were published. The results contained in these two studies (Allan et al., 1966, and Hermann et al., 1966) are directly comparable with the findings of the present study since similar methods of data collection and of

MEAN VOICE VOLUME

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD.DEV. | MEAN | STD.DEV | | |
| PA | 63.5250 | 6.6429 | 67.9399 | 5.7233 | 19 | -5.1783** |
| PE | 64.3888 | 6.0465 | 68.2000 | 6.8850 | 8 | -3.0807** |
| PA+OP | 64.0250 | 6.9929 | 63.5999 | 5.7025 | 7 | 0.2854 |
| PE+OP | 60.0166 | 4.3180 | 62.3499 | 2.8989 | 5 | -1.5761 |
| GROUP | 63.3092 | 6.2619 | 66.4069 | 5.9937 | 42 | -3.9036** |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 10.2500 | 1 | 10.2500 | 0.2552 |
| SURGERY | 20.8125 | 1 | 20.8125 | 0.5182 |
| INTERACTION | 49.3750 | 1 | 49.3750 | 1.2293 |
| ERROR | 1566.4375 | 39 | 40.1651 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT
(ADJUSTED SUMS OF SQUARES OF MAIN EFFECTS)

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.6515 | 1 | 0.6515 | 0.0200 |
| SURGERY | 225.7140 | 1 | 225.7140 | 6.9246* |
| INTERACTION | 5.0360 | 1 | 5.0360 | 0.1545 |
| ERROR | 1271.2500 | 39 | 32.5961 | |

TABLE 19

measuring "voice volume" were used. The Allan and the Hermann studies both found that stereotactically induced subcortical lesions lead to a significant diminution from pre-operative voice volume levels. In 1968 Bell confirmed that in the immediate post-operative period patients do speak much softer than they had prior to surgery. However, Bell also found that during the first three weeks after surgery the voice volume of his patient group gradually increased. In some cases voice volume had returned to its pre-operative level. The present finding that eleven years after surgery operated patients speak as loudly as unoperated patients appears to support Bell's view that the diminution in voice volume seen in the immediate post-operative period is transitory.

After treatment the mean voice volume level for the group as a whole was 66.41± 5.99 dB. The mean voice volume levels of the four subgroups are shown in TABLE 19A. Analysis of variance of these after treatment measures revealed that surgery was a highly significant factor ($F=6.9246$, $d.f.=1,39$; $p<.05$). Operated patients spoke far softer than their unoperated counterparts. No difference in voice volume, however, was found between paralysis agitans and post-encephalitic patients. (See TABLE 19C).

The before and after treatment voice volume measures were compared to ascertain the effect of L-dopa treatment. With treatment, the group as a whole showed a significant increase in voice volume ($t= -3.9036$; $d.f.=42$; $p<.005$). However, when the group was divided into its constituent

parts it was clear that not all the four subgroups reflected this change. Only the unoperated subgroups, i.e. PA and PE, showed a significant increase in voice volume. Of the unoperated subgroups, PE+OP tended to speak marginally louder and PA+OP marginally softer after treatment. Taken together, the operated subgroups showed no change at all (see TABLE 19A).

On the basis of these results it is clear that the effect of stereotactic surgery in depressing voice volume levels is not completely 'transitory'. When the voice volume levels of patients who had undergone surgery eleven years previously are compared with the voice volume levels of unoperated, severely akinetic, Parkinsonian patients, no statistically significant difference is found. However, when operated and unoperated patients are on maximal dosages of L-dopa, only unoperated patients are seen to benefit. Voice volume levels of unoperated patients increase substantially with treatment, while operated patients show no such improvement. Clearly, stereotactic subcortical surgery *does* have an important and a lasting effect on voice volume level: it reduces the capacity for improvement.

## VARIATION IN VOICE VOLUME

According to Darley et al. (1968b) 'monoloudness' is one of the characteristic disturbances in the speech of Parkinsonian patients. The degree of monoloudness is reflected in the variance of the voice volume measures. These variances were analysed to see whether the degree

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD.DEV. | MEAN | STD.DEV. | | |
| PA | 2.4715 | 1.1515 | 2.5520 | 1.1424 | 18 | -0.5395 |
| PE | 1.7398 | 1.2183 | 2.1660 | 0.9831 | 7 | -1.2862 |
| PA+OP | 2.1930 | 0.6908 | 2.7718 | 0.9386 | 5 | -1.8545 |
| PE+OP | 1.9358 | 1.2698 | 2.6766 | 1.0246 | 5 | -1.0142 |
| GROUP | 2.1962 | 1.416 | 2.5256 | 1.0446 | 38 | -2.0179* |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 3.0279 | 1 | 3.0279 | 2.3701 |
| SURGERY | 0.3010 | 1 | 0.3010 | 0.2356 |
| INTERACTION | 0.1845 | 1 | 0.1845 | 0.1444 |
| ERROR | 44.7153 | 35 | 1.2775 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.4362 | 1 | 0.4362 | 0.3895 |
| SURGERY | 0.6839 | 1 | 0.6839 | 0.6107 |
| INTERACTION | 0.4340 | 1 | 0.4340 | 0.3876 |
| ERROR | 39.1943 | 35 | 1.1198 | |

TABLE 20

of subcortical damage and/or whether dopamine replacement therapy had any influence on monoloudness.

Before treatment, no significant variation in the magnitude of voice volume variances was found either between operated and unoperated patients, or between paralysis agitans and post-encephalitic Parkinsonian patients. The results of this analysis of variance are shown in TABLE 20A.

The after treatment data presented a similar picture. As can be seen from TABLE 20B surgical history and type of Parkinsonism were not associated with significantly different degrees of monoloudness.

When the before and after treatment voice volume variances were compared, it was clear that for the group as a whole there had been a significant increase in the variability of loudness. Furthermore, as can be seen in TABLE 20A the spread of these measurements had decreased. The four subgroups all reflected these changes (see TABLE 20C) despite the fact that none of the changes reached the 5% level of confidence.

From these findings it may be concluded that neither before nor after treatment does the degree of variability in loudness vary significantly with the degree of subcortical damage. However, variability in loudness *is* affected by dopamine level. Once replacement therapy had reached an optimal level (as defined on clinical criteria) a significant increase in the variability of loudness was seen. *All* patients, irrespective of type of Parkinsonism or surgical history, showed this improvement.

## SUSTAINED PHONATION

Before treatment had begun the group as a whole were, on average, able to sustain phonation for 7.227± 3.79 seconds. TABLE 21A shows the length of time for which each of the four subgroups could sustain phonation. Canter (1961) found a "marked reduction in this aspect of physiological support for speech" in his group of seventeen (unoperated) paralysis agitans patients. They could sustain phonation for about 11.6 seconds while his control group averaged 20.6 seconds. The patients in the present study appeared even more impaired on this task than Canter's patients had been. It seems, however, that Canter's patients were also only slightly to moderately affected in other respects. As was mentioned in Chapter 4, although he did not assess the severity of akinesia in his patients, Canter did mention that they were all fully mobile and able to walk to his laboratory. In the present study all the patients were found by the neurologist in charge to be severely akinetic. Perhaps the disparity between Canter's measurements and the present (study's) findings is a reflection of this difference in degree of general or 'clinical' impairment.

Analysis of variance of these before treatment measures of sustained phonation revealed that neither type of Parkinsonism nor surgical history was an important factor. The length of sustained phonation did not vary significantly with either of these two factors. (See TABLE 21B).

SUSTAINED PHONATION

A.COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | | |
|---|---|---|---|---|---|---|
| | MEAN | STD.DEV. | MEAN | STD.DEV. | DF | F |
| PA | 7.3535 | 3.8182 | 9.3580 | 4.5308 | 19 | -1.9803* |
| PE | 5.7755 | 3.0228 | 8.1548 | 2.9535 | 8 | -2.8039** |
| PA+OP | 7.3512 | 4.5885 | 8.6587 | 3.6931 | 7 | -2.6176** |
| PE+OP | 8.8167 | 3.7736 | 9.8317 | 3.1105 | 5 | -0.9036 |
| GROUP | 7.2270 | 3.7899 | 9.0421 | 3.8349 | 42 | -3.0308** |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 1.2754 | 1 | 1.2745 | 0.0875 |
| SURGERY | 11.7522 | 1 | 11.7522 | 0.8060 |
| INTERACTION | 21.5414 | 1 | 21.5414 | 1.4773 |
| ERROR | 568.6768 | 39 | 14.5815 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 1.0859 | 1 | 1.0859 | 0.0702 |
| SURGERY | 0.3015 | 1 | 0.3015 | 0.0195 |
| INTERACTION | 12.6194 | 1 | 12.6194 | 0.8153 |
| ERROR | 603.6682 | 39 | 15.4787 | |

D. ANALYSIS OF COVARIANCE

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.1338 | 1 | 0.1338 | 0.0127 |
| SURGERY | 2.2173 | 1 | 2.2173 | 0.2102 |
| INTERACTION | 0.5708 | 1 | 0.5708 | 0.0541 |
| ERROR | 400.7874 | 38 | 10.5470 | |

TABLE 21

After treatment had reached an optimal level for each patient, the group of patients as a whole were able to sustain phonation, on average, for 9.042± 3.83 seconds. (See TABLE 21A above for the mean values of sustained phonation for the individual subgroups.) Analysis of variance showed that after treatment the length of sustained phonation did not vary significantly either with type of Parkinsonism or with surgical history. (See TABLE 21C).

When the before and after treatment measures of sustained phonation were compared, it was seen that the group as a whole was able to sustain phonation significantly longer after treatment ($t = -3.0308$, $d.f. = 42$; $p < .005$). The four subgroups all reflected this increase (see TABLE 21A), although in the smallest subgroup (PE+OP) the increase did not reach significance. Analysis of covariance confirmed that the degree of improvement did not vary with either type of Parkinsonism or surgical history. (See TABLE 21D.)

From these results it may be concluded that the ability to sustain phonation is not affected either by type of Parkinsonism or by surgical history. With treatment, all four subgroups show similar degrees of improvement. After treatment, the ability to sustain phonation does not vary significantly with either type of Parkinsonism or with surgical history.

# TEMPORAL CHARACTERISTICS

## READING RATE

Before treatment the group of patients read, on average, 152.79 words per minute. The standard deviation of this mean was found to be 36.76 w.p.m. This relatively large variation in reading speed is not totally unexpected. Darley et al. (1968b), for example, found, in their investigation of dysarthrias, that their group of (untreated) Parkinsonian patients was considered by the three judges to contain both slow and fast speakers. Canter, in his extensive study (1961) of the speech characteristics of (untreated) Parkinsonian patients, included 'rate of reading' amongst his test parameters. He found that although the median reading rate of his 17 patients was 172.6 w.p.m. and that of his 17 age-matched controls was 177.6 w.p.m., the range of reading rates for his patients was three and a half times larger than that for his controls. Although Canter himself does little more statistically with his carefully collected data, he does provide complete records of his results. From his records the average reading rate for his patients was calculated by the present writer to be 154.88± 46.11 w.p.m. and that of his controls to be 180.66± 15.27 w.p.m.

Out of interest, Canter's data and the data from the present investigation were compared. Cochran's

t-approximation was used in preference to the usual t-test for independent samples for a number of reasons. The two sets of data were based on different standard reading passages (Fairbank's "Rainbow Passage" by Canter, the British version of Johnson's "Arthur the Rat" by Gamsu). All sets of data were collected and analysed by different investigators, etc. The advantage of Cochran's t is that it is more conservative than the Behrens-Fisher solution (Snedecor and Cochran, 1956) and is robust enough to be used with samples from even markedly skewed populations. Using Cochran's t, it was found that there was no significant difference between the reading rate obtained from Canter's patients and the untreated patients in the present study (Cochran's t= .16, t(0.05) = 2.0927). Furthermore, Canter's control group read significantly faster than his own patients (Cochran's t = 2.1883, t(0.05) = 2.11) and the untreated patients in the present study (Cochran's t = 3.7693, t(0.05) = 1.5556). FIGURE 20 shows Canter's patient and control data together with the data from the present investigation.

The mean reading rates obtained for each of the four subgroups before treatment are contained in TABLE 22A. Analysis of variance showed that rate of reading varied significantly neither with type of Parkinsonism nor with surgical history. (See TABLE 22B.)

After treatment, the group of patients as a whole read, on average, 167.33 w.p.m. A standard deviation of 36.70 w.p.m. was obtained. The value of this deviation is remarkably similar to the standard deviation obtained

RATE OF READING: COMPARISON OF DATA BY CANTER (1961) AND FROM THE PRESENT INVESTIGATION

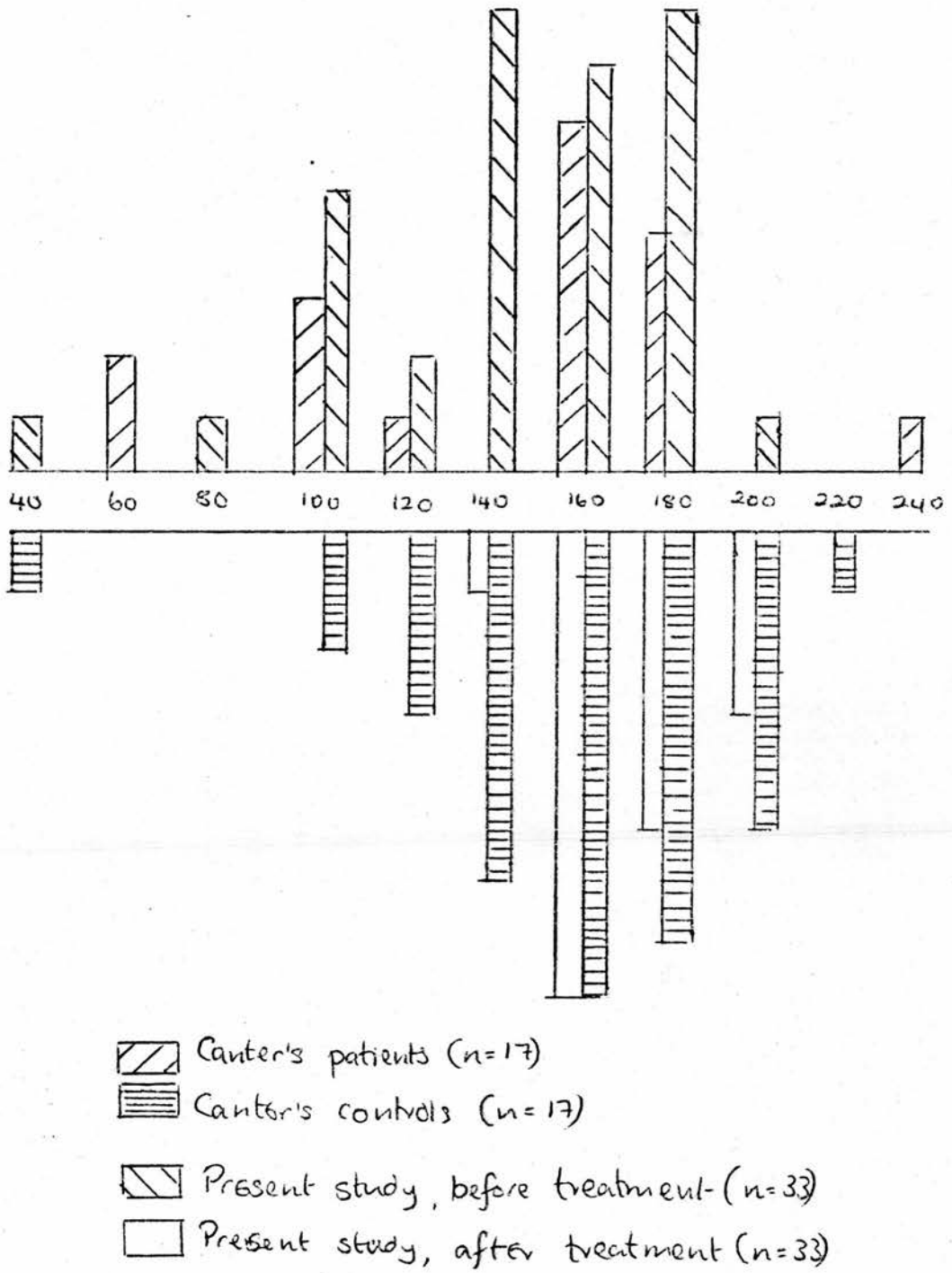



FIGURE 20

RATE OF READING

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 161.7363 | 33.1058 | 171.1863 | 38.3924 | 15 | -1.4301 |
| PE | 149.3943 | 34.5000 | 172.6686 | 24.8100 | 6 | -2.6500** |
| PA+OP | 159.0583 | 37.4720 | 168.9833 | 32.1501 | 5 | -0.9473 |
| PE+OP | 121.3600 | 42.9975 | 145.4980 | 51.5134 | 4 | -2.4437* |
| GROUP | 152.7850 | 36.7600 | 167.3250 | 36.7000 | 33 | -3.4000** |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 4212.6952 | 1 | 4212.6952 | 3.2355 |
| SURGERY | 1918.6032 | 1 | 1918.6032 | 1.4736 |
| INTERACTION | 404.9595 | 1 | 404.9595 | 0.3110 |
| ERROR | 39060.4596 | 30 | 1302.0153 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 662.6385 | 1 | 662.6385 | 0.4779 |
| SURGERY | 1322.0576 | 1 | 1322.0576 | 0.9534 |
| INTERACTION | 852.3182 | 1 | 852.3182 | 0.6147 |
| ERROR | 41598.5477 | 30 | 1386.6183 | |

TABLE 22

before treatment. Analysis of variance carried out on the after treatment reading rate revealed that rate of reading did not vary significantly with either of the two factors. (See TABLE 22C).

On comparing the before and after treatment reading rates for the group as a whole, a significant increase in rate was found ($t = 3.4526$; $d.f. = 33$; $p < .0025$). All four subgroups showed an increase in reading rate although in only two subgroups (PE and PE+OP) did this increase reach at least the 5% level. (See TABLE 22A). Of particular interest is the comparison between treated patients and Canter's control group. As reported above, before treatment the group of patients as a whole were found to read significantly slower than Canter's control. After treatment, however, these same patients read as fast as Canter's controls. (Cochran's $t = .9667$, $t(0.05) = 2.0928$). (See FIGURE 20).

## PERIODICITY OF SPEECH

The results concerning the length of pauses and phonations in unoperated paralysis agitans patients have been discussed elsewhere (Mawdsley and Gamsu, 1971 - see appendix). In that study only a few post-encephalitic and a few operated patients were included. It appeared from those results, however, that unoperated paralysis agitans patients differ from post-encephalitic and operated patients in respect of the parameters in question.

The corpus of data on which the paper was based has therefore been extended to include more patients in these latter categories. The corpus now presented comprises data from all four subgroups, that is, PA, PE, PA+OP and PE+OP. This extended corpus of data will be discussed from three viewpoints - the length of phonations, the length of pauses, and the ratio between phonations and pauses.

## LENGTH OF PHONATIONS

Before treatment the mean length of words for the group as a whole was 353± 113ms. TABLE 23A contains the mean value for the phonations of the individual subgroups. Analysis of variance revealed no differences of significance between paralysis agitans and post-encephalitic patients or between operated and unoperated patients. (See TABLE 23B).

After treatment the group's mean length of phonations was 351± 83ms. The mean length of phonations for the four subgroups are contained in TABLE 23A. Analysis of variance after treatment revealed, once again, that neither type of Parkinsonism nor surgical history affects the length of phonations. (See TABLE 23C).

On comparing the length of phonations before and after treatment for the group as a whole, no significant change was found ($t = 0.1048$; $d.f. = 33$; $p > .05$). When the group was divided into its constitutent parts it was seen that in only one subgroup, subgroup PA, was there a significant change in length of phonation. (See TABLE 23A).

MEAN LENGTH OF PHONATIONS

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 404 | 121 | 353 | 92 | 13 | 2.5079* |
| PE | 313 | 95 | 333 | 73 | 8 | -0.7204 |
| PA+OP | 299 | 102 | 346 | 61 | 5 | -0.9448 |
| PE+OP | 348 | 97 | 397 | 109 | 4 | -1.3242 |
| GROUP | 353 | 113 | 351 | 83 | 33 | 0.1048 |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 7.0110 | 1 | 7.0110 | 1.4890 |
| SURGERY | 6.4531 | 1 | 6.4531 | 1.3705 |
| INTERACTION | 13.6515 | 1 | 13.6515 | 2.8993 |
| ERROR | 141.2576 | 30 | 4.7086 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.0061 | 1 | 0.0061 | 0.0021 |
| SURGERY | 1.0835 | 1 | 1.0835 | 0.3729 |
| INTERACTION | 2.6600 | 1 | 2.6600 | 0.9154 |
| ERROR | 87.1711 | 30 | 2.9057 | |

TABLE 23

The length of phonation for subgroup PA was significantly shorter after treatment ($t = 2.5079$; $d.f.=13$; $p<.05$). The other subgroups, however, both individually, and when grouped together failed to show a significant change.

The variability of each patient's phonations was also considered. Before treatment the standard deviations for individual patients gave a mean value of $2.17 \pm 839$ ms. TABLE 24A contains the mean values for the subgroups. Analysis of variance revealed no significant variation in the size of this deviation with either type of Parkinsonism or surgical history (see TABLE 24B). After treatment, the standard deviations of individual patients gave a mean value for the group as a whole of $2.03 \pm 593$ ms. The mean values after treatment for the subgroups are contained in TABLE 24A. Analysis of variance after treatment also revealed no significant variation with either type of Parkinsonism or surgical history (see TABLE 24C). On comparing the before and after treatment standard deviations of the group as a whole no significant change in the magnitude of deviations was found ($t=0.7914$; $d.f.= 33$; $p>.05$). Of the four subgroups, subgroup PA was the only subgroup to show a significant change. The standard deviations for subgroup PA were significantly reduced after treatment ($t=2.3565$, $d.f.= 13$; $p<.05$). The three other subgroups, however, showed no change in the variability of their phonation times.

LENGTH OF PAUSES

The mean length of pauses for the group as a whole

## VARIATION IN LENGTH OF PHONATIONS

### A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 2.5914 | 0.8272 | 2.0329 | 0.4459 | 13 | 2.3565* |
| PE | 1.7511 | 0.7065 | 1.7533 | 0.3998 | 8 | -0.0074 |
| PA+OP | 1.9750 | 0.9590 | 2.4700 | 0.8621 | 5 | -1.3182 |
| PE+OP | 1.9880 | 0.5625 | 1.9660 | 0.7325 | 4 | 0.0512 |
| GROUP | 2.1715 | 0.8387 | 2.0262 | 0.5928 | 33 | 0.7914 |

### B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.5905 | 1 | 0.5905 | 0.9446 |
| SURGERY | 2.6830 | 1 | 2.6830 | 4.2922* |
| INTERACTION | 1.1858 | 1 | 1.1858 | 1.8970 |
| ERROR | 18.7530 | 30 | 0.6351 | |

### C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.7480 | 1 | 0.7480 | 2.3072 |
| SURGERY | 0.9226 | 1 | 0.9226 | 2.8458 |
| INTERACTION | 0.2000 | 1 | 0.2000 | 0.6169 |
| ERROR | 9.7258 | 30 | 0.3242 | |

TABLE 24

before treatment was 408± 244ms. The mean length of pauses for the four subgroups are contained in TABLE 25A. Analysis of variance revealed no significant variation in pause length with either type of Parkinsonism or surgical history. (See TABLE 25B).

After treatment the mean length of pauses for the group as a whole was 372± 247 ms. The mean length of pauses for the four subgroups are contained in TABLE 25A. Analysis of variance showed that the length of pauses did not vary significantly with either type of Parkinsonism or surgical history. (See TABLE 25C).

On comparing the length of pauses before and after treatment for the group as a whole, no significant change was detected. When the four subgroups were considered individually, however, it was seen that subgroup PA did undergo a significant change. After treatment the length of their pauses had *increased* significantly ($t = -3.2292$; $d.f. = 13$; $p < .001$). Subgroup PE and subgroup PA+OP were shown to have made no significant change. Subgroup PE+OP, however, did change with treatment. With treatment the length of the pauses had almost halved. This change just failed to reach the .05 level of significance ($t = 2.7546$; $d.f. = 4$; $p > .05$. $t(.05) = 2.776$).

The variability of individual patient's pauses was also considered. The standard deviation from each patient in the group provided a mean value of 124± 66ms. The mean values for the four subgroups are contained in TABLE 26A. The magnitude of standard deviation did not vary with either type of Parkinsonism or surgical history.

## MEAN LENGTH OF PAUSES

### A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 410 | 149 | 462 | 228 | 13 | -3.2292*** |
| PE | 399 | 145 | 335 | 205 | 8 | 1.2175 |
| PA+OP | 375 | 285 | 338 | 252 | 5 | 1.8620 |
| PE+OP | 410 | 285 | 229 | 180 | 4 | 2.7546 |
| GROUP | 408 | 244 | 372 | 247 | 33 | 0.0500 |

### B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.0063 | 1 | 0.0063 | 0.0004 |
| SURGERY | 0.7894 | 1 | 0.7894 | 0.0449 |
| INTERACTION | 1.6384 | 1 | 1.6384 | 0.0932 |
| ERROR | 527.1674 | 30 | 17.5722 | |

### C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 59.6609 | 1 | 59.6609 | 2.6015 |
| SURGERY | 69.7086 | 1 | 69.7086 | 3.0396 |
| INTERACTION | 14.1514 | 1 | 14.1514 | 0.6171 |
| ERROR | 688.0000 | 30 | 22.9333 | |

TABLE 25

VARIATION IN LENGTH OF PAUSES

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 2.5829 | 1.4076 | 2.4186 | 0.7909 | 13 | 0.5000 |
| PE | 2.4622 | 0.7627 | 1.7256 | 0.6941 | 8 | 2.8960* |
| PA+OP | 2.6500 | 2.1498 | 2.0433 | 0.7106 | 5 | 0.8580 |
| PE+OP | 2.0760 | 0.7618 | 1.8980 | 1.3305 | 4 | 0.4188 |
| GROUP | 2.4874 | 1.3146 | 2.0924 | 0.8616 | 33 | 2.2100* |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.2096 | 1 | 0.2096 | 0.1127 |
| SURGERY | 0.6895 | 1 | 0.3708 | 0.3708 |
| INTERACTION | 0.2888 | 1 | 0.2888 | 0.1553 |
| ERROR | 55.7900 | 30 | 1.8597 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.2154 | 1 | 0.2154 | 0.2293 |
| SURGERY | 2.2170 | 1 | 2.2170 | 3.0809 |
| INTERACTION | 0.4716 | 1 | 0.4716 | 0.6554 |
| ERROR | 21.5866 | 30 | 0.7196 | |

TABLE 26

(See TABLE 26B). After treatment, the standard deviation obtained from each patient provided a group mean value of 105± 43ms. On comparing the before and after treatment measures of variability, it was found that the group as a whole showed a significant decrease in variability with treatment. All four subgroups showed similar reductions in variability although only the reduction shown by subgroup PE reached significance. (See TABLE 26A). As can be seen from the subgroup means in TABLE 26A, paralysis agitans patients tended to vary the length of their pauses more than post-encephalitic Parkinsonian patients. On analysis, however, this difference did not reach the 5% significance level. As is shown in TABLE 26C, analysis of variance found that the magnitude of the standard deviation of pauses varied significantly neither with type of Parkinsonism, nor with surgical history.

## RATIO OF PHONATIONS TO PAUSES

In addition to the length of phonations and the length of pauses, the ratio between these two measures was also considered. The phonation-pause ratio was calculated for each patient in the group. The mean value of these ratios for the group was found to be 1.1982± .78. The mean values for the four subgroups are contained in TABLE 27A. Analysis of variance of these measures showed that the magnitude of the ratio did not vary significantly with either type of Parkinsonism or surgical history. (See TABLE 27B).

RATIO OF PHONATIONS TO PAUSES

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 1.4414 | 0.9780 | 0.8386 | 1.5610 | 13 | 2.9849* |
| PE | 0.9140 | 0.5520 | 1.3267 | 0.8377 | 8 | -2.7083* |
| PA+OP | 1.0733 | 0.5922 | 1.4217 | 0.6721 | 5 | -1.4735 |
| PE+OP | 1.1860 | 0.6693 | 2.3240 | 1.3653 | 4 | -2.3727 |
| GROUP | 1.1982 | 0.7803 | 1.2891 | 0.9135 | 33 | -0.5655 |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.0883 | 1 | 0.0883 | 0.1438 |
| SURGERY | 0.8561 | 1 | 0.8561 | 1.3944 |
| INTERACTION | 0.7257 | 1 | 0.7257 | 1.1819 |
| ERROR | 18.4210 | 30 | 0.6140 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 4.7892 | 1 | 4.7892 | 7.4738* |
| SURGERY | 3.6897 | 1 | 3.6897 | 5.7580* |
| INTERACTION | 0.1640 | 1 | 0.1640 | 0.2559 |
| ERROR | 19.2232 | 30 | 0.6408 | |

TABLE 27

After treatment the mean phonation to pause ratio for the group as a whole was found to be 1.2891± .91. The mean values for the four subgroups are contained in TABLE 27A. Analysis of variance after treatment showed that the magnitude of phonation to pause ratios varied significantly with both surgical history and type of Parkinsonism. (See TABLE 27C). Paralysis agitans patients were found to have smaller phonation-pause ratios than post-encephalitic patients. This indicates that paralysis agitans patients, compared to post-encephalitic patients, have shorter phonations separated by longer pauses. Similarly, unoperated patients were found to have smaller phonation-pause ratios than operated patients, i.e., that unoperated patients had shorter words and longer pauses than operated patients.

On comparing the ratios obtained before and after treatment it was found that no significant change had occurred for the group as a whole. Subgroup PA, however, showed a significant *decrease* in phonation-pause ratios ($t= 2.9849$; $d.f.= 13$; $p<.05$). Of the three other subgroups, however, only subgroup PE and subgroup PA+OP showed significant changes. In both cases it was found that the ratios had *increased* significantly. Subgroup PE+OP however did not show a significant change, although this group too showed an *increase* in phonation-pause ratios. Not surprisingly, therefore, when these three groups, that is PE, PA+OP and PE+OP, are considered together, a *significant increase* in phonation-pause ratios is obtained ($t= -3.5361$; $d.f.= 19$; $p<.01$).

## THE REGULARITY OF SPEECH

The recordings of the patients counting from 1 to 10 were further analysed to see whether the recited numbers were evenly spaced in time, or whether counting speeded up towards the end of the sequence, i.e. whether there was evidence of festination.

For this analysis the lengths of both words and pauses were taken into account. The times that elapsed between the first phonemes of the successive words (i.e. numeral-names) were measured. These measures thus comprised the time taken to say a number plus the pause following it, before the next number was begun. Nine such measures were obtained; "ten" had to be omitted since, as it was the last word in the sequence, no estimate of the pause succeeding it could be made.

The nine word-pause units from the before and after treatment recordings of the patients' counting were subjected to similar analyses of variance using a 2x2x9 model, where the first factor (A) is surgery; the second (B), type of Parkinsonism; and, the third (C), the nine word-pause units.

Before treatment neither surgery ($F=.0003$; $d.f.= 1.31$) nor type of Parkinsonism ($F=.0725$; $d.f.= 1.31$) affected the length of word-pause units. Furthermore, there was no significant interaction between surgery and type of Parkinsonism ($F=.0389$; $d.f.= 1.31$). A highly significant main effect for factor C (i.e., length of the nine word-pause units) was found ($F= 4.9623$; $d.f.= 8.248$;

MULTIFACTOR REPEATED MEASURE ANALYSIS OF VARIANCE OF THE BEFORE TREATMENT WORD - PAUSE DATA

| SOURCE | DF | SS | MS | F |
|---|---|---|---|---|
| Between subjects | 34 | 9760.4608 | | |
| A (surgery) | 1 | 0.8731 | 0.8731 | 0.0003 |
| B (type of Parkinsonism) | 1 | 239.3295 | 239.3295 | 0.0725 |
| AB | 1 | 128.3799 | 128.3799 | 0.0389 |
| Error between subjects | 31 | 9391.8783 | 302.9681 | |
| Within subjects | 280 | 2096.4372 | | |
| C(Word - pause units) | 8 | 266.1794 | 33.2724 | 4.9623* |
| AC | 8 | 70.9710 | 8.8714 | 1.3231 |
| BC | 8 | 51.3180 | 6.4148 | 0.9567 |
| ABC | 8 | 45.1306 | 5.6413 | 0.8414 |
| Error within subjects | 248 | 1662.8282 | 6.7050 | |
| ANALYSIS OF LINEAR TREND | | | | |
| Within subjects | 35 | 526.4931 | | |
| C | 1 | 233.2000 | 233.2000 | 25.7673** |
| AC | 1 | 8.3646 | 8.3646 | 0.9242 |
| BC | 1 | 3.4442 | 3.4442 | 0.3806 |
| ABC | 1 | 0.9274 | 0.9275 | 0.1025 |
| Error within subjects | 31 | 280.5569 | 9.0502 | |
| ANALYSIS OF QUADRATIC TREND | | | | |
| Within subjects | 35 | 301.1240 | | |
| C | 1 | 5.1255 | 8.1255 | 0.5577 |
| AC | 1 | 0.8881 | 0.8881 | 0.0966 |
| BC | 1 | 8.5045 | 8.5045 | 0.9254 |
| ABC | 1 | 1.7179 | 1.7179 | 0.1869 |
| Error within subjects | 31 | 284.8880 | 9.1899 | |

TABLE 28

p <.01). This is clear indication of a marked discrepancy between these nine units. Hence the analysis indicated that before treatment the patients' counting is far from evenly spaced. None of the interactions with factor C is statistically significant, indicating that the shapes of the acceleration curves are essentially similar for operated and unoperated groups, and for paralysis agitans and post-encephalitic groups.

These findings are in accord with the judges' evaluations of speech recordings. As was reported in Chapter 7, the judges found that the patients' speech was characterized by festination and that there were no differences in degree of festination amongst the four subgroups.

The nature of this variation among the nine word-pause units was investigated. The results of this analysis of trend are summarized in TABLE 28. As can be seen, 87.61% of the sum of squares for factor C (ss=266.1974) are accounted for by the sum of squares for the linear component (ss=233.2000). Not surprisingly, this linear regression was found to be highly significant (F=25.7673; d.f.= 1,31; p<.01). The linear component on which this sum of squares is based was negative, indicating a downward trend, i.e., the lengths of the word-pause units grew progressively shorter throughout the sequence of nine units. No significant degree of curvature was found in this negative regression (F=0.5577; d.f.= 1,31).

After treatment, results were obtained that are essentially similar to those obtained from the before

MULTIFACTOR REPEATED MEASURE ANALYSIS OF VARIANCE OF THE AFTER TREATMENT WORD-PAUSE DATA

| SOURCE | DF | SS | MS | F |
|---|---|---|---|---|
| Between subjects | 35 | 8745.3636 | | |
| A (surgery) | 1 | 58.9517 | 58.9517 | 0.2192 |
| B (type ) | 1 | 74.4980 | 74.4980 | 0.2770 |
| AB | 1 | 5.4763 | 5.4763 | 0.0204 |
| Error between subjects | 32 | 8606.4376 | 268.9606 | |
| Within subjects | 288 | 1658.2533 | | |
| C (word-pause units) | 8 | 129.5513 | 16.1939 | 2.9983** |
| AC | 8 | 48.1159 | 6.0145 | 1.1136 |
| BC | 8 | 19.8457 | 2.4807 | 0.4593 |
| ABC | 8 | 78.0681 | 9.7585 | 1.8065 |
| Error within subjects | 256 | 1382.6723 | 5.4011 | |
| ANALYSIS OF LINEAR TREND | | | | |
| Within subjects | 36 | 379.1097 | | |
| C | 1 | 110.9760 | 110.9760 | 14.0942** |
| AC | 1 | 0.6601 | 0.6601 | 0.0838 |
| BC | 1 | 7.0112 | 7.0112 | 0.8904 |
| ABC | 1 | 8.4979 | 8.4979 | 1.0792 |
| Error within subjects | 32 | 251.9645 | 7.8739 | |
| ANALYSIS OF QUADRATIC TREND | | | | |
| Within subjects | 36 | 108.3028 | | |
| C | 1 | 2.9750 | 2.9750 | 0.9171 |
| AC | 1 | 0.0209 | 0.0209 | 0.0064 |
| BC | 1 | 1.0976 | 1.0976 | 0.3384 |
| ABC | 1 | 0.4087 | 0.4087 | 0.1260 |
| Error within subjects | 32 | 103.8006 | 3.2438 | |

TABLE 29

treatment analysis. No differences in overall length of word-pause units was found. Neither factor A (surgery) nor nor factor B (type of Parkinsonism) appeared to have a significant effect on the overall length of word-pause units. Moreover there were no significant interactions between these two main factors. (See TABLE 29).

A significant variation in length among the nine word-pause units was found ($F=2.9983$, $d.f.=8,256$; $p<.01$). Thus, after treatment, as had been the case before treatment, a marked discrepancy in the lengths of the nine word-pause units was found. On testing the effect of the other main factors (A and B) on word-pause length (Factor C), no significant interactions were found. Thus, neither surgery nor type of Parkinsonism affected the variation in word-pause length. However, when the large overall interaction between surgery, type of Parkinsonism and word'pause units (i.e. "ABC") was tested, it failed to reach significance ($F(.05)$ 1.98). The magnitude of ABC was not completely unexpected. It will be remembered that the judges rated the degree of festination shown by operated post-encephalitic patients more severely than any of the other three groups. As pointed out in Chapter 7, the variation in these ratings of festination after treatment, varied significantly with both type of Parkinsonism and surgical history. The present findings are clearly consonant with the judges' impressions.

On further analysis it was found that 85.66% of the sums of squares for factor C ($ss= 129.5513$) was accounted for by the linear component ($ss= 110.9760$). As can be

seen in TABLE 29, this linear regression was highly significant. As had been the case before treatment, the linear component on which this sums of squares is based was negative. This shows that even after treatment, the patients' speech was festinant. The length of the word-pause units grew progressively shorter throughout the sequence of nine word-pause units. This finding is in keeping with the judges' evaluations of the speech recordings of these patients (see Chapter 6). No significant degree of curvature was found in the negative regression of factor C ($F = 0.9171$, d.f.= 1,32).

In order to assess whether L-dopa treatment had any effect on festination, the slopes of the before and after treatment linear regressions were calculated and compared. Linear regressions were fitted to the mean length of the word-pause units by the least squares method. (Regression lines for only the group as a whole were fitted since the previous analyses had revealed no significant variation with type of Parkinsonism or surgical history). The analyses of variation in TABLE 30 summarize the results of fitting lines to the data. The slope of the before treatment regression was found to be -11.69; and the slope of the after treatment regression was found to be -8.16. The difference between these slopes, however, was not found to be significant. ($t=1.6923$, d.f.= 14, $p>.05$). This finding corroborates the judge's opinion of no decrement in the degree of festination.

ANALYSES OF VARIANCE: LINEAR REGRESSION OF LENGTH OF WORD PAUSE UNITS ON SERIAL POSITION

| SOURCE OF VARIATION | SS | DF | F |
|---|---|---|---|
| *Before treatment* | | | |
| DEVIATIONS DUE TO REGRESSION | 8199.3660 | 1 | 49.5366 |
| DEVIATIONS FROM REGRESSION | 1158.6490 | 7 | |
| TOTAL VARIATION | 9358.0150 | 8 | |
| *After treatment* | | | |
| DEVIATIONS DUE TO REGRESSION | 3995.1360 | 1 | 41.8208 |
| DEVIATIONS FROM REGRESSION | 668.7090 | 7 | |
| TOTAL VARIATION | 4663.8450 | 8 | |

TABLE 30

# CHAPTER 9

## RESULTS IV: THE INITIATION OF SPEECH

In Chapter 5 it was postulated that akinesia affects not only the description of movement, but also its initiation. The previous two chapters dealt with experimental findings related to the *description* of a complex motor-sequence such as speech. This chapter is concerned with the *initiation* of speech. Reported here are the results of tests of the initiation of 'automatic' speech sequences and of confrontation naming. Also reported are the results from a small battery of standard psychological tests.

* * *

As Oldfield and Wingfield pointed out in their description of the Object Naming Test, their Test is a useful technique, but it is not a standardized test. No set of norms exists for confrontation naming. For this reason, a small group of males, matched for age and I.Q.

with the patients, were used as "controls". The group were all volunteers, drawn from the pool of servitors at Edinburgh University. (All thirteen of the men refused payment for their participation). The group were screened for neurological disorders. They were all right-handed and English was their mother-tongue. (None in fact was bilingual). The test was administered in the same way with the controls as with the patients.

## METHODS OF ANALYSIS

The measurements of the initiation of 'automatic' speech sequences were analysed using the same methods as those used on the data discussed in the preceding chapter. Briefly, this involved subjecting the before and after treatment data to analyses of variance to test whether type of Parkinsonism or surgical history, i.e. different degrees of subcortical damage, were associated with different levels of performance. The differences between the before and after treatment data was tested by means of t-tests (for paired samples) in order to see whether a reduction in akinesia after treatment is reflected in a reduction of latency in the initiation of 'automatic' speech sequences.

The data from the confrontation naming test was analysed by different methods. Four aspects of the

initiation of responses were considered:-

1. *Success in naming test items:* The number of test-items correctly named by each subject ("success score") was calculated and $\chi^2$ tests were used to test whether patients were as successful as the controls, both before and after treatment. The purpose of this analysis was to ascertain whether a reduction in word-availability was associated with Parkinsonism.

2. *Error analysis:* The types of error made both by patients and controls were analysed using $\chi^2$ tests to see whether patients and controls differed both in terms of gross number of errors made and in terms of the relative proportions of the different types of error. Similar analyses were carried out to see whether type of Parkinsonism, surgical history and/or L-dopa treatment affected the gross number and/or the type of errors made by the patients.

3. *Speed of response:* The speed with which patients and controls responded to the twenty-six test items was compared. It was of interest to find out whether untreated patients were slower than the controls in naming objects; whether patients responded faster after treatment than they had previously, before treatment; and whether, after treatment, patients responded as fast as did the controls. Also of interest was whether type of Parkinsonism and/or surgical history affected the patients' speed of response (before and after treatment).

The twenty-six items of the Object Naming Test fall naturally into seven classes. These classes are defined by the frequency of occurrence of the object name (according to the Thorndike-Lorge listing). The mean response latency for each of these classes was calculated for the group as a whole and for the four subgroups, under both the test and re-test conditions. Means were also calculated for the controls. Had the data been homogeneous, it would have been suitable for treatment by t-tests. However, this was not the case (see later). A normal transformation of the data was necessary, and the difference between the magnitude of the various sets of means was tested using a u-statistic. This transformation and statistic is explained more fully when the results of the analysis are presented.

4. *The nature of the disturbance to the initiation of motor sequences:* The basic hypothesis of the present investigation is that speech disorders consequent upon basal ganglia lesions are akinetic in nature. Akinesia, it is further hypothesized, is non-specific and affects the initiation (and description) of *all* motor sequences. Thus it will affect speaking, writing, walking, playing the piano, and so on. Furthermore, it will affect all forms of these activities. For example, in speech, akinesia will delay the initiation of any utterance, be it 'automatic' or highly propositional in character.

The Oldfield Wingfield Object Naming Test provides data eminently suitable for testing this hypothesis. As

explained above, the test comprises twenty-six outline drawings of objects. The objects depicted include both common and rare items. A number of workers (for example, Howes, 1964; Rochford and Williams, 1965) have demonstrated a temporal relationship between response availability and frequency of occurrence of the name of the depicted object; commonly used words are 'retrieved' faster than rarely used words. Furthermore, Oldfield and co-workers have shown that a linear relationship subsists between the response latency and the logarithmic frequency of the object name. Thus, if akinesia does in fact effect a constant delay in the initiation of all responses to the Object Naming Test, and if L-dopa treatment does ameliorate or reverse this effect, then it may be predicted that:-

a. the *slopes* of the linear regressions obtained from the controls, from the group of patients as a whole before treatment, and from the group of patients after treatment will be similar;

b. the *intercepts* of these three regressions will differ. Furthermore, it may be predicted that i) the before treatment intercept will be significantly larger than the after treatment intercept and the control intercept (i.e., before treatment patients respond slower over the whole test than they do after treatment, or than the controls do); ii) the after treatment and the control intercepts will not differ significantly (i.e., with treatment, patients will respond as fast to the whole test as do the controls).

Since the data was found to be non-homogeneous, weighted linear regressions were fitted (see later for a more detailed description of the weighting), and the regressions were compared using an analysis of covariance (similar to that described by Snedecor and Cochran, 1967). Similar analyses were also carried out in which the performance of each of the four subgroups both before and after treatment was compared with that of the controls.

## INITIATION OF 'AUTOMATIC' SPEECH SEQUENCES

Both before and after treatment the patients were asked to recite a number of "automatic" speech sequences - counting from "1" to "10", the names of the days of the week, the months of the year, and the alphabet. The time between the command to begin and the beginning of the first word in each sequence was measured. Average "initiation times" were calculated for each patient , one for before treatment, the other for after treatment.

Before treatment, the group of patients as a whole took 1.245$\pm$492 ms. to begin these "automatic" sequences. As Table 31A shows, the mean initiation times for the four subgroups ranged from 1.377$\pm$479 ms. (for subgroup PE) to 1.174$\pm$867 ms. (for subgroup PE+OP). Analysis of variance revealed no significant differences between the subgroups: neither type of Parkinsonism nor surgical history was associated with slower or faster initiation of 'automatic'

## INITIATION OF 'AUTOMATIC' SPEECH SEQUENCES

### A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 1.2123 | 0.4209 | 0.6771 | 0.2422 | 17 | 4.1585** |
| PE | 1.3770 | 0.4786 | 0.7885 | 0.1757 | 6 | 0.4255 |
| PA+OP | 1.2307 | 0.4366 | 0.8394 | 0.2224 | 6 | 2.2354* |
| PE+OP | 1.1736 | 0.8667 | 1.0130 | 0.1841 | 4 | 0.7394 |
| GROUP | 1.2453 | 0.4918 | 0.7743 | 0.2416 | 37 | 3.2782* |

### B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.0564 | 1 | 0.0564 | 0.2188 |
| SURGERY | 0.0258 | 1 | 0.0258 | 0.1001 |
| INTERACTION | 0.1031 | 1 | 0.1031 | 0.3999 |
| ERROR | 8.7670 | 34 | 0.2578 | |

### C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.1432 | 1 | 0.1432 | 2.9224 |
| SURGERY | 0.2724 | 1 | 0.2724 | 5.5591** |
| INTERACTION | 0.0630 | 1 | 0.0630 | 1.2857 |
| ERROR | 1.6178 | 33 | .0490 | |

TABLE 31

sequences. (See TABLE 31B).

Analysis of variance after treatment revealed that surgical history was highly significant. Patients who had undergone surgery were far slower than patients who had not. Whether patients were diagnosed as having paralysis agitans or post-encephalitic Parkinsonism was irrelevant as far as speed of initiation was concerned: no significant difference was found between the two types of Parkinsonism. (See TABLE 31C).

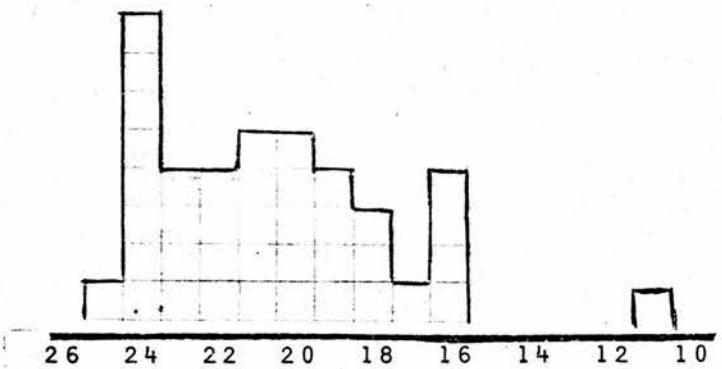
On testing the difference between the before and after treatment initiation times it was found that the group of patients as a whole responded significantly faster after treatment ($t=3.2782$ $d.f.=37$; $p<.01$). Although all four subgroups responded faster after treatment, only in the case of the two paralysis agitans subgroups did this reach significance (*PA*: $t=4.1585$, $d.f.=17$, $p<.01$; *PA+OP*: $t=2.2354$; $d.f.=6$; $p<.01$. In the two post-encephalitic subgroups the "improvement" shown did not reach the .05 per cent level for the one-tailed tests. (See TABLE 31A).

## THE NAMING OF OBJECTS

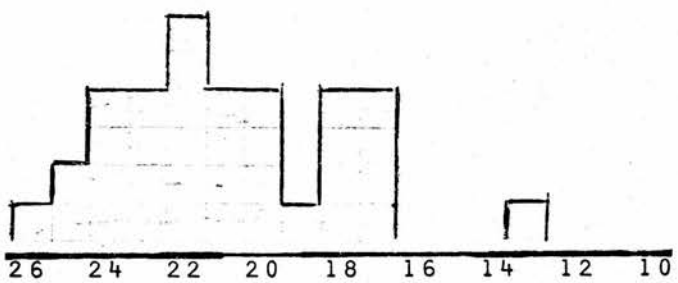
### SUCCESS IN NAMING OBJECTS

The number of test-items correctly named by a subject

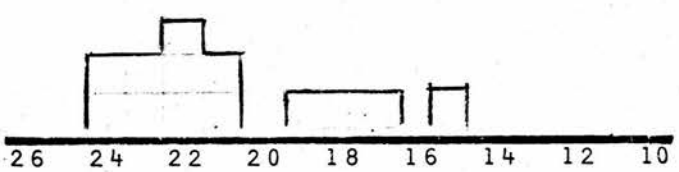
DISTRIBUTION OF 'SUCCESS SCORES'




*Before treatment*




*After treatment*




*Controls*

FIGURE 21

constituted a 'success score'. The distributions of these scores for the patients before and after treatment are shown in FIGURE 21. Also shown is the distribution of scores for the controls.

The median score of the control group was 21.00 and this was used as a cut-off point to classify the distribution of patients' scores. Before treatment no significant differences were revealed either between the four subgroups, or between the patients and the controls. Similarly, after treatment no significant differences in distribution were detected between either the four sub-groups, or between the patients and the controls.

It may therefore be concluded that the patients, both before and after treatment, were as successful as the controls in correctly naming test-items. Furthermore, from these findings it may be inferred that on retest, once L-dopa treatment had reached an optimal level, there was no significant change in the patients' performance; they were as successful after treatment as they had been before treatment in correctly naming test-items.

## ERRORS IN NAMING OBJECTS

The erroneous responses were classified according to whether the stimulus was misidentified, misnamed or not known. Misidentification was scored if the subject described the stimulus as another object (XYLOPHONE → table).

A misnaming error was scored if the subject described the function of the stimulus-item (GYROSCOPE → "oh! it's for checking balance....it's used on ships to steady them..."); if a subject produced a response which morphologically approximated to the correct response (OCTOPUS → "octopoctopus"); or, if the subject produced a response standing in the semantic relationship of synecdoche (OCTOPUS → "tentacles") or of metonymy (TUNINGFORK → "pitch") to the stimulus-item. When the subject said he did not know what the object was, the error was scored as 'not known'.

The distribution of the three types of error (represented as percentages) for the four subgroups before and after treatment, and for the controls are shown in TABLE 32. No significant differences in the relative proportions of types of error were found between

DISTRIBUTION OF TYPES OF ERROR

| SOURCE | BEFORE TREATMENT | | | AFTER TREATMENT | | |
|---|---|---|---|---|---|---|
| | *Misnaming* (%) | *Misidentification* (%) | *Not known* (%) | *Misnaming* (%) | *Misidentification* (%) | *Not known* (%) |
| PA | 24 | 38 | 38 | 26 | 31 | 43 |
| PE | 32 | 48 | 20 | 35 | 35 | 30 |
| PA+OP | 24 | 38 | 38 | 23 | 37 | 40 |
| PE+OP | 24 | 41 | 35 | 39 | 44 | 17 |
| CONTROLS | 33 | 33 | 34 | - | - | - |

TABLE 32

the four subgroups and controls, either before ($\chi^2$=5.2217, d.f.=8) or after treatment ($\chi^2$=7.0603, d.f.=8). From these sets of results it may be inferred that no significant change occurred in the relative proportions of types of error of the patients before and after treatment.

Error analysis of this kind has previously been successfully used in differentiating between patients with language disorders and controls. Newcombe et al. (1971) in a study of patients with chronic, focal brain lesions due to missile injury tested their subjects on the same Object Naming Test (using the same procedure). The errors made by subjects were analysed using the same criteria of classification. They found significant differences in the relative proportions of types of error between patients and controls. Moreover, they found over 70% of errors made by patients with left temporal lobe lesions were misnaming errors. Misidentification errors were far less common, and tended to occur more frequently in their bilateral group patients with lesions of the occipital areas of the brain.

In the present study, the similarity of the relative proportions of error types between patients and controls is interesting. It tends to rule out both qualitative language disturbance in untreated patients, and qualitative change with treatment. Furthermore, it is particularly interesting that patients who had previously undergone subcortical surgery did not stand out from the other patients. Previous studies (reviewed in Chapter 4) have

reported dysphasia and anomia following subcortical surgery. The present results, in failing to reveal any deficit, clearly indicate that if these patients had suffered adverse effects from surgery, these effects were transitory and left no detectable residual anomia.

The relationship between stimulus item and the number of errors was also considered. TABLES 33 to 37 show the distribution of errors according to stimulus item.

DISTRIBUTION OF ERRORS ACCORDING TO STIMULUS ITEM FOR SUBGROUP PA

| STIMULUS | BEFORE TREATMENT | | | | AFTER TREATMENT | | | |
|---|---|---|---|---|---|---|---|---|
| | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* |
| xylophone | 7 | 2 | 3 | 2 | 10 | 1 | 8 | 1 |
| gyroscope | 10 | 3 | 0 | 7 | 10 | 2 | 1 | 7 |
| metronome | 10 | 1 | 2 | 7 | 11 | 1 | 3 | 7 |
| syringe | 4 | 0 | 2 | 2 | 5 | 0 | 2 | 3 |
| stethescope | 4 | 0 | 3 | 1 | 5 | 0 | 2 | 3 |
| tuningfork | 9 | 2 | 4 | 3 | 8 | 2 | 2 | 4 |
| octopus | 5 | 2 | 3 | 0 | 7 | 4 | 2 | 1 |
| horseshoe | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| anvil | 4 | 1 | 0 | 3 | 3 | 1 | 0 | 2 |
| dice | 2 | 0 | 2 | 0 | 2 | 0 | 2 | 0 |
| microscope | 8 | 3 | 2 | 3 | 7 | 4 | 0 | 3 |
| windmill | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| typewriter | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| screw | 5 | 1 | 4 | 0 | 1 | 1 | 0 | 0 |
| anchor | 1 | 0 | 1 | 0 | 3 | 3 | 0 | 0 |
| basket | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| book | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 74 | 18 | 28 | 28 | 72 | 19 | 22 | 31 |

TABLE 33

DISTRIBUTION OF ERRORS ACCORDING TO STIMULUS ITEM FOR SUBGROUP PE

| STIMULUS | BEFORE TREATMENT | | | | AFTER TREATMENT | | | |
|---|---|---|---|---|---|---|---|---|
| | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* |
| xylophone | 4 | 0 | 2 | 2 | 3 | 0 | 2 | 1 |
| gyroscope | 5 | 1 | 0 | 4 | 5 | 0 | 0 | 5 |
| metronome | 5 | 1 | 2 | 2 | 3 | 0 | 2 | 1 |
| syringe | 3 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| stethescope | 5 | 0 | 4 | 1 | 3 | 0 | 2 | 1 |
| tuningfork | 4 | 2 | 0 | 2 | 3 | 1 | 1 | 1 |
| bagpipe | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| octopus | 2 | 2 | 0 | 0 | 2 | 2 | 0 | 0 |
| horseshoe | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| anvil | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| dice | 4 | 0 | 4 | 0 | 4 | 1 | 3 | 0 |
| microscope | 3 | 0 | 1 | 2 | 2 | 0 | 0 | 2 |
| windmill | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 |
| typewriter | 1 | 1 | 0 | 0 | 2 | 1 | 1 | 0 |
| screw | 2 | 1 | 1 | 0 | 1 | 1 | 0 | 0 |
| | 42 | 10 | 16 | 16 | 30 | 7 | 11 | 12 |

TABLE 34

DISTRIBUTION OF ERRORS ACCORDING TO STIMULUS ITEM FOR SUBGROUP PA+OP

| STIMULUS | BEFORE TREATMENT | | | | AFTER TREATMENT | | | |
|---|---|---|---|---|---|---|---|---|
| | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* |
| xylophone | 4 | 0 | 2 | 2 | 4 | 0 | 3 | 1 |
| gyroscope | 5 | 4 | 0 | 1 | 4 | 3 | 0 | 1 |
| metronome | 5 | 2 | 2 | 1 | 4 | 1 | 1 | 2 |
| syringe | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| tuningfork | 0 | 0 | 0 | 0 | 2 | 0 | 1 | 1 |
| octopus | 2 | 2 | 0 | 0 | 2 | 2 | 0 | 0 |
| horseshoe | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| anvil | 2 | 1 | 0 | 1 | 2 | 1 | 0 | 1 |
| dice | 2 | 0 | 2 | 0 | 1 | 1 | 0 | 0 |
| microscope | 4 | 0 | 3 | 1 | 4 | 0 | 2 | 2 |
| screw | 4 | 0 | 4 | 0 | 1 | 1 | 0 | 0 |
| drum | 1 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
| tap | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| book | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| | 32 | 10 | 16 | 6 | 26 | 9 | 9 | 8 |

TABLE 35

DISTRIBUTION OF ERRORS ACCORDING TO STIMULUS ITEM FOR SUBGROUP PE+OP

| STIMULUS | BEFORE TREATMENT | | | | AFTER TREATMENT | | | |
|---|---|---|---|---|---|---|---|---|
| | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* |
| xylophone | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 |
| gyroscope | 3 | 2 | 0 | 1 | 2 | 1 | 1 | 0 |
| metronome | 3 | 1 | 2 | 0 | 2 | 1 | 1 | 0 |
| syringe | 2 | 0 | 1 | 1 | 1 | 0 | 1 | 0 |
| stethescope | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| tuningfork | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| octopus | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 |
| dice | 1 | 0 | 1 | 0 | 2 | 0 | 2 | 0 |
| typewriter | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 |
| screw | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| tap | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| book | 2 | 0 | 2 | 0 | 0 | 0 | 0 | 0 |
| | 17 | 4 | 7 | 6 | 12 | 6 | 5 | 1 |

TABLE 36

DISTRIBUTION OF ERRORS ACCORDING TO STIMULUS ITEM FOR THE CONTROLS

| STIMULUS ITEM | *Total nos.* | *Mis-naming* | *Misiden-tification* | *Not known* |
|---|---|---|---|---|
| gyroscope | 9 | 2 | 1 | 6 |
| microscope | 7 | 4 | 0 | 3 |
| stethescope | 6 | 0 | 4 | 2 |
| octopus | 4 | 3 | 0 | 1 |
| xylophone | 5 | 4 | 0 | 1 |
| metronome | 10 | 2 | 5 | 3 |
| tuningfork | 9 | 4 | 2 | 3 |
| syringe | 1 | 0 | 0 | 1 |
| anvil | 3 | 0 | 1 | 2 |
| typewriter | 1 | 1 | 0 | 0 |
| drum | 2 | 2 | 0 | 0 |
| bagpipes | 2 | 0 | 2 | 0 |
| screw | 2 | 1 | 0 | 1 |
| | 61 | 23 | 15 | 23 |

TABLE 37

Kendall's coefficient of concordance (W) was calculated to reveal the extent of agreement across groups concerning the degree of difficulty presented by individual test-items. The before treatment data gave a W of .7150. This corresponds to a $\chi^2$ of 89.375 with 25 degrees of freedom, indicating an extremely high degree of concordance ($p<.001$). Similarly, the after treatment data gave a W of .7769, corresponding to a $\chi^2$ of 77.693 with 25 degrees of freedom ($p<.001$). Rank order correlations for the overall difficulty of the twelve most difficult items were calculated for all groups and subgroups. (See TABLE 38).

RANK ORDER CORRELATION (KENDALL'S) BETWEEN NUMBER OF ERRORS AND LOGARITHMIC FREQUENCY OF THE STIMULUS ITEM

| | PRE | | POST | |
|---|---|---|---|---|
| | τ | z | τ | z |
| PA | 0.6052 | 4.3354*** | 0.6434 | 4.6089*** |
| PE | 0.7489 | 5.3646*** | 0.5934 | 4.2815*** |
| PA+OP | 0.3508 | 2.5130*** | 0.5209 | 3.7314*** |
| PE+OP | 0.3955 | 2.8334*** | 0.6004 | 4.3009*** |
| CONTROLS | 0.5984 | 4.2865*** | | |

TABLE 38

Both before and after treatment the patient group as a whole and the four subgroups showed high and significantly *positive* correlations. The less frequent the name of the depicted object, the greater the failure rate. Similar

results were obtained for the controls.

It may therefore be concluded that success or failure on this Object Naming Test is strongly dependent on the nature of the test-item. Failure to name objects was not dependent on whether the subject was a patient or a control since both patients and controls experienced similar difficulty with the less frequent test-items.

## LATENCY IN NAMING OBJECTS (CORRECTLY)

The latency measures of the (correct) responses were grouped into seven categories according to the Thorndike Lorge count of the stimulus item which elicited them (the method employed by Newcombe et al., 1965). Means and variances were calculated for each of the seven categories for all groups and subgroups. The variances of responses, however, were found to differ significantly across the seven categories within all groups and subgroups (In all cases, Bartlett's test, $p<.01$). Furthermore, the variances were significantly different between the controls and patient groups and subgroups (Snedecor's F-test, $p<.05$). Comparisons between mean response latencies for controls and patients were therefore made using the standard normal deviate of the differences between the mean latencies for each frequency category. Summing these normal deviates over all the categories ($g=7$) a statistic U is obtained which can be used to test the null hypothesis

that there is no difference between the controls' and patients' mean latencies - i.e. the hypothesis that U comes from a normal distribution with a mean 0, and a variance g, N(0,g).

Using this technique a significant difference was found between the mean latencies for the controls and for the group of untreated patients. Similar significant differences were found between the controls and the PRE mean latencies for all four subgroups. (See TABLE 39).

STANDARD NORMAL DEVIATES: PRE vs CONTROLS

| SOURCE | U-STATISTIC | HYPOTHESIS | P |
|---|---|---|---|
| PA | 15.7286 | N(0,7) | <.01 |
| PE | 13.1200 | N(0,7) | <.01 |
| PA+OP | 11.3816 | N(0,7) | <.01 |
| PE+OP | 7.3641 | N(0,7) | <.01 |
| GROUP AS A WHOLE | 16.6777 | N(0,7) | <.01 |

TABLE 39

In all cases the U statistic obtained was positive. This indicates that in all comparisons, the controls were significantly faster in responding to the stimulus items than were the patients.

Comparisons were also made between the controls' mean latencies and the patients' mean latencies after treatment. It was found that after treatment the group of patients as a whole were still significantly slower in responding than the controls. However, as TABLE 40 shows,

STANDARD NORMAL DEVIATES: POST vs CONTROLS

| SOURCE | U-STATISTIC | HYPOTHESIS | p |
|---|---|---|---|
| PA | .6133 | N(0,7) | >.05 |
| PE | .2354 | N(0,7) | >.05 |
| PA+OP | .9549 | N(0,7) | >.05 |
| PE+OP | 9.8010 | N(0,7) | <.01 |
| GROUP AS A WHOLE | 5.3900 | N(0,7) | <.05 |

TABLE 40

this is entirely attributable to subgroup PE+OP. All three other subgroups responded as fast as did the controls; subgroup PE+OP, however, remained significantly slower. From the results contained in TABLES 39 and 40 it can be inferred that all patients except post-encephalitic Parkinsonian patients who had previously undergone subcortical surgery improved with treatment on this task. After treatment they were as fast as the controls in response.

## RESPONSE LATENCY AND FREQUENCY OF OCCURRENCE OF STIMULUS ITEM

Wingfield (1966) and Oldfield and Wingfield (1964) demonstrated that a linear relationship subsists between the response latency and the logarithmic frequency of

occurrence of the words in the Object Naming Test. Since, in the present study, in each and every group and subgroup the variance of mean response latencies for all twenty-six test-items were found to differ significantly (Bartlett's test, $p<.01$), *weighted* linear regressions were fitted. The weights were calculated by the formula $\frac{n_i}{\text{pooled variance}}$, where $n_i$ is the number of responses in the group to the $_i$th object, and the pooled variance is estimated from all the patients' responses to the object.

Regression lines were fitted to only part of the test items. Arbit et al. (1970) have shown that only tests above a certain level of difficulty reveal psychological deficit in Parkinsonian patients. Since psychological functions are not of particular interest in this part of the analysis of performance, difficult test items were avoided. Thus the possibility of any psychological deficits clouding the issue was carefully avoided. "Easy items" were operationally defined as those items which had elicited more than 95% correct responses. This established a cut-off point at the frequency level of 10 per million, and defined fourteen such "easy items". These included items such as "SHOE"; "BASKET"; "GLOVE"; and, "SCREW". The cut-off point proved felicitously stringent. Newcombe et al. (1976) had shown that test-items with a log. frequency of $10^{-5.10}$ were particularly sensitive to the psycholinguistic effects in patients with brain lesions. The cut-off point adopted in the present study lies well within the 'non-sensitive' area of the test.

Comparisons between the regression lines of the controls and the patients (as a whole) before and after treatment were made using analyses of covariance. These results are presented in TABLE 43. The table shows clearly the series of successive analyses that were carried out. Initially three regression lines, one for each set of data, were fitted (TABLES 41, 42 and 43A). Parallel lines were then fitted to the same data sets and the difference between the fitting of separate and of parallel lines was tested. This, in effect, is a test of the differences in *slope* of the three lines. As TABLE 43B shows, no significant difference was found. The data sets could be described equally well by either separate or parallel lines. It is apparant therefore that, for the group as a whole, neither Parkinsonian lesion/lesions nor L-dopa treatment have *qualitative* effects on the confrontation naming of "easy" objects.

Next, *quantitative* differences between the three lines were considered. One line was fitted to the three data sets and the difference between the fitting of one line and the fitting of parallel lines was tested. This is a test of the differences in *intercepts* of the three regression lines. If all three lines were of comparable height, no difference should be found between the fitting of one line or of two parallel lines. As TABLE 43C shows, the fitting of one line to all three data sets did make a considerable difference; the three lines clearly do not represent similar levels of performance.

ANALYSES OF VARIANCE: FITTING WEIGHTED LINEAR REGRESSIONS OF RESPONSE LATENCY ON LOGARITHMIC FREQUENCY OF THE OBJECT NAME FOR THE GROUP AS A WHOLE BEFORE AND AFTER TREATMENT AND FOR THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | F |
|---|---|---|---|
| *For The GROUP AS A WHOLE BEFORE TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 109.7778 | 33.8956** |
| DEVIATION FROM REGRESSION | 12 | 38.8645 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 148.6423 | |
| *For The GROUP AS A WHOLE AFTER TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 58.3368 | 14.2160* |
| DEVIATION FROM REGRESSION | 12 | 49.2429 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 107.5797 | |
| *For The CONTROLS:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 46.8913 | 20.6079** |
| DEVIATION FROM REGRESSION | 12 | 27.3044 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 74.1957 | |

* $p<.05$
** $p<.01$

TABLE 41

WEIGHTED LINEAR REGRESSION FOR THE GROUP OF PATIENTS AND THE CONTROLS

| SOURCE | REGRESSION |
|---|---|
| GROUP OF PATIENTS BEFORE TREATMENT | $y = -1.48 - 0.56x$ |
| GROUP OF PATIENTS AFTER TREATMENT | $y = -0.99 - 0.42x$ |
| CONTROLS | $y = -0.76 - 0.35x$ |

TABLE 42

ANALYSIS OF COVARIANCE: COMPARISONS OF WEIGHTED LINEAR REGRESSIONS FROM THE GROUP AS A WHOLE BEFORE TREATMENT, AFTER TREATMENT, AND FROM THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | MS | F |
|---|---|---|---|---|
| A. FITTING THREE LINES | 3 | 215.0059 | 71.6686 | 22.3552** |
| DEVIATIONS FROM 3 LINES | 36 | 115.4118 | 3.2059 | |
| WITHIN GROUP | 39 | 330.4177 | | |
| B. FITTING // LINES | 1 | 206.8123 | 206.8123 | 64.5099** |
| IMPROVEMENT OVER 3 LINES | 2 | 8.1936 | 4.0968 | 1.2779 |
| DEVIATIONS FROM 3 LINES | 36 | 115.4118 | 3.2059 | |
| WITHIN GROUPS | 39 | 330.4177 | | |
| C. FITTING ONE LINE | 1 | 205.5811 | 205.5811 | 63.2013** |
| IMPROVEMENT OVER // LINES | 2 | 74.2781 | 37.1391 | 11.4176** |
| DEVIATIONS FROM // LINES | 38 | 123.6054 | 3.2528 | |
| TOTAL | 41 | 403.4646 | | |
| D. FITTING // LINES | 1 | 206.8123 | 206.8123 | 63.5798** |
| DEVIATIONS FROM // LINES | 38 | 123.6054 | 3.2528 | |
| BETWEEN GROUPS:- | | | | |
| PRE : POST+CONTROLS | 1 | 66.1354 | 66.1354 | 20.3320** |
| POST : CONTROLS | 1 | 6.9114 | 6.9114 | 2.1248 |
| TOTAL | 41 | 403.4646 | | |

**p<.01

TABLE 43

LINEAR REGRESSIONS FOR THE GROUP AS A WHOLE

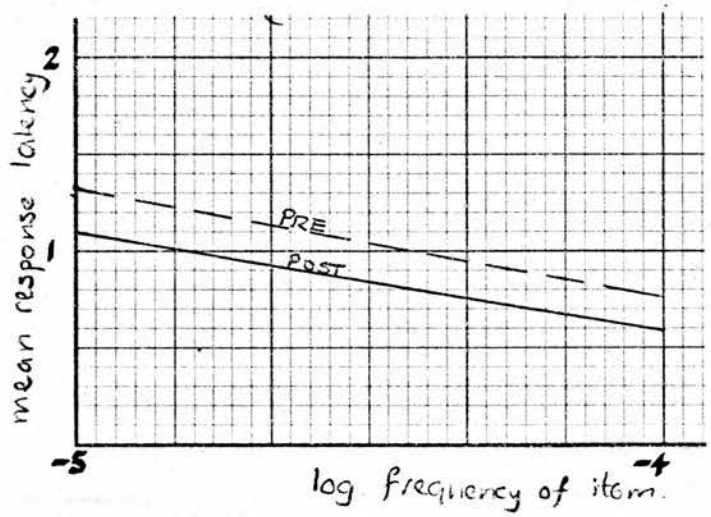



FIGURE 22

LINEAR REGRESSION FOR THE CONTROLS

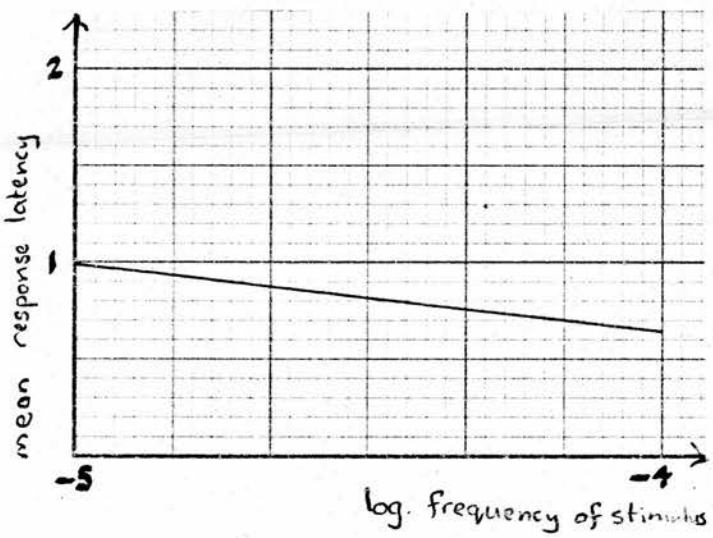



FIGURE 23

Finally, multiple comparisons between the three intercepts were carried out. It was found that there was no difference between the intercepts of the regression lines for the patients after treatment and for the controls. This clearly indicates that treated patients respond just as fast as the controls. There was, however, a significant difference between the intercept of the line for the treated patients plus the controls. (See TABLE 43D). The intercept of the regression line for the untreated patients was far larger than the intercepts of the other two lines. Thus the performance of the patients before treatment was considerably worse than their performance after treatment and worse than the performance of the controls.

From this series of analyses the following conclusions may be drawn:

a. Over and above the effect that log. frequency of the test-item has on the response latency, Parkinsonian lesions exert a constant, quantitative effect on the confrontation naming of "easy" objects. (Untreated) Parkinsonian patients are significantly slower in responding.

b. L-dopa treatment effects a uniform reduction in the latency of response to confrontation naming *without* alerting the rate of increase of the latency of response with the logarithmic frequency of the item.

In short, as predicted in the basic hypothesis of this investigation the results show that Parkinsonism and L-dopa have quantitative, and not qualitative, effects on the performance of subjects in a confrontation naming test.

Similar analyses were carried out in which the before and after treatment performances of each of the four subgroups were compared with that of the controls. These analyses are summarized in TABLES 44 through to 55. From these tables it may be seen that:-

a. in each and every set of data a linear relationship subsisted between response latency and logarithmic frequency of the object name (TABLES 44, 45; 47, 48; 50, 51; 53, 54).

b. no significant difference in the *slope* of the regression lines was found. Thus, it may be concluded from these findings (TABLES 46B, 49B 52B, 55B) that the nature of the behaviour tested was not affected by type of Parkinsonism and/or surgical history and/or L-dopa treatment.

c. significant differences in the *intercept* of the regression lines were found (TABLES 46C, 49C, 52C, 55C). It was also found that the four subgroups did not all perform comparably; subgroup PE+OP once again, stood out.

The after treatment intercepts for subgroups PA, PE, PA+OP were found to be similar to the control intercept. Their before treatment intercepts, however, were found to be significantly larger than their after treatment intercept and that of the controls. These findings indicate that before treatment each of these three groups did display impairment in a confrontation naming task. The impairment is shown to be a uniform increase in response latency. With treatment a uniform reduction in response

ANALYSES OF VARIANCE: FITTING WEIGHTED LINEAR REGRESSIONS OF RESPONSE LATENCY ON THE LOGARITHMIC FREQUENCY OF THE OBJECT NAME FOR SUBGROUP PA BEFORE AND AFTER TREATMENT AND FOR THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | F |
|---|---|---|---|
| *For SUBGROUP PA BEFORE TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 67.3213 | 24.6553** |
| DEVIATION FROM REGRESSION | 12 | 32.7659 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 100.0872 | |
| *For SUBGROUP PA AFTER TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 37.5846 | 9.1784* |
| DEVIATION FROM REGRESSION | 12 | 49.1383 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 86.7229 | |
| *For CONTROLS:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 46.8913 | 20.6079** |
| DEVIATION FROM REGRESSION | 12 | 27.3044 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 74.1957 | |

* $p<.05$
** $p<.01$

TABLE 44

WEIGHTED LINEAR REGRESSION FOR SUBGROUP PA AND THE CONTROLS

| SOURCE | REGRESSION |
|---|---|
| SUBGROUP PA BEFORE TREATMENT | $y = -1.48 - 0.56x$ |
| SUBGROUP PA AFTER TREATMENT | $y = -0.99 - 0.42x$ |
| CONTROLS | $y = -0.76 - 0.35x$ |

TABLE 45

ANALYSIS OF COVARIANCE: COMPARISONS OF WEIGHTED LINEAR REGRESSIONS FROM SUBGROUP PA BEFORE TREATMENT, AFTER TREATMENT, AND FROM THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | MS | F |
|---|---|---|---|---|
| FITTING THREE LINES | 3 | 151.7972 | 50.5991 | 16.6796** |
| DEVIATIONS FROM 3 LINES | 36 | 109.2086 | 3.0336 | |
| WITHIN GROUPS | 39 | 261.0058 | | |
| FITTING // LINES | 1 | 142.3776 | 142.3776 | 46.9335** |
| IMPROVEMENT OVER 3 LINES | 2 | 9.4196 | 4.7098 | 1.5525 |
| DEVIATIONS FROM 3 LINES | 36 | 109.2086 | 3.0336 | |
| WITHIN GROUPS | 39 | 261.0058 | | |
| FITTING ONE LINE | 1 | 143.9153 | 143.9153 | 46.1001** |
| IMPROVEMENT OVER // LINES | 2 | 33.7784 | 16.8892 | 5.4101** |
| DEVIATIONS FROM // LINES | 38 | 118.6282 | 3.1218 | |
| TOTAL | 41 | 296.3219 | | |
| FITTING // LINES | 1 | 142.3776 | 142.3776 | 45.6075** |
| DEVIATIONS FROM // LINES | 38 | 118.6282 | 3.1218 | |
| BETWEEN GROUPS:- | | | | |
| PRE : POST+CONTROLS | 1 | 34.6692 | 34.6692 | 11.1055** |
| POST : CONTROLS | 1 | 0.6469 | 0.6469 | 0.2072 |
| TOTAL | 41 | 296.3219 | | |

**p .01

TABLE 46

ANALYSES OF VARIANCE: FITTING WEIGHTED LINEAR REGRESSIONS OF RESPONSE LATENCY ON THE LOGARITHMIC FREQUENCY OF THE OBJECT NAME FOR SUBGROUP PE BEFORE AND AFTER TREATMENT AND FOR THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | F |
|---|---|---|---|
| *For SUBGROUP PE BEFORE TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 39.8707 | 33.1207** |
| DEVIATION FROM REGRESSION | 12 | 14.4453 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 54.3160 | |
| *For SUBGROUP PE AFTER TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 12.2349 | 6.1961* |
| DEVIATION FROM REGRESSION | 12 | 23.6957 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 35.9306 | |
| *For CONTROLS:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 46.8913 | 20.6079** |
| DEVIATION FROM REGRESSION | 12 | 27.3044 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 74.1957 | |

* $p<.05$
** $p<.01$

TABLE 47

WEIGHTED LINEAR REGRESSIONS FOR SUBGROUP PE AND THE CONTROLS

| SOURCE | REGRESSION |
|---|---|
| SUBGROUP PE BEFORE TREATMENT | $y = -2.24 - 0.76x$ |
| SUBGROUP PE AFTER TREATMENT | $y = -2.18 - 0.47x$ |
| CONTROLS | $y = -0.76 - 0.35x$ |

TABLE 48

ANALYSIS OF COVARIANCE: COMPARISONS OF WEIGHTED LINEAR REGRESSIONS FROM SUBGROUP PE BEFORE TREATMENT, AFTER TREATMENT, AND FROM THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | MS | F |
|---|---|---|---|---|
| FITTING THREE LINES | 3 | 98.9969 | 32.9990 | 18.1523** |
| DEVIATIONS FROM 3 LINES | 36 | 65.4454 | 1.8179 | |
| WITHIN GROUPS | 39 | 164.4423 | | |
| FITTING // LINES | 1 | 89.0601 | 89.0601 | 48.9906** |
| IMPROVEMENT OVER 3 LINES | 2 | 9.9368 | 4.9685 | 2.7330 |
| DEVIATIONS FROM 3 LINES | 36 | 65.4454 | 1.8179 | |
| WITHIN GROUPS | 39 | 164.4423 | | |
| FITTING ONE LINE | 1 | 86.2477 | 86.2477 | 43.4782** |
| IMPROVEMENT OVER // LINES | 2 | 52.0792 | 26.0396 | 13.1268** |
| DEVIATIONS FROM // LINES | 38 | 75.3822 | 1.9837 | |
| TOTAL | 41 | 213.7091 | | |
| FITTING // LINES | 1 | 89.0601 | 89.0601 | 44.8960** |
| DEVIATIONS FROM // | 38 | 75.3822 | 1.9837 | |
| BETWEEN GROUPS:- | | | | |
| PRE : POST+CONTROLS | 1 | 44.2034 | 44.2034 | 22.2833** |
| POST : CONTROLS | 1 | 5.0634 | 5.0634 | 2.5525 |
| TOTAL | 41 | 213.7091 | | |

**p .01

TABLE 49

ANALYSES OF VARIANCE: FITTING WEIGHTED LINEAR REGRESSIONS OF THE RESPONSE LATENCY ON THE LOGARITHMIC FREQUENCY OF THE OBJECT NAME FOR SUBGROUP PA+OP BEFORE AND AFTER TREATMENT AND FOR THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | F |
|---|---|---|---|
| *For SUBGROUP PA+OP BEFORE TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 7.4326 | 18.9752** |
| DEVIATION FROM REGRESSION | 12 | 4.7002 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 12.3828 | |
| *For SUBGROUP PA+OP AFTER TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 5.9282 | 8.1994* |
| DEVIATION FROM REGRESSION | 12 | 8.6755 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 14.6037 | |
| *For CONTROLS:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 46.8913 | 20.6079** |
| DEVIATION FROM REGRESSION | 12 | 27.3044 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 74.1957 | |

* p<.05
** p<.01

TABLE 50

WEIGHTED LINEAR REGRESSION FOR SUBGROUP PA+OP AND CONTROLS

| SOURCE | REGRESSION |
|---|---|
| SUBGROUP PA+OP BEFORE TREATMENT | y = -0.58 - 0.34x |
| SUBGROUP PA+OP AFTER TREATMENT | y = -0.54 - 0.31x |
| CONTROLS | y = -0.76 - 0.35x |

TABLE 51

ANALYSIS OF COVARIANCE: COMPARISONS OF WEIGHTED LINEAR REGRESSIONS FROM SUBGROUP PA+OP BEFORE TREATMENT, AFTER TREATMENT, AND FROM THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | MS | F |
|---|---|---|---|---|
| FITTING THREE LINES | 3 | 60.2521 | 20.0840 | 17.7735** |
| DEVIATIONS FROM 3 LINES | 36 | 40.6801 | 1.1300 | |
| WITHIN GROUPS | 39 | 100.9322 | | |
| FITTING // LINES | 1 | 60.1477 | 60.1477 | 53.2281** |
| IMPROVEMENT OVER 3 LINES | 2 | 0.1044 | 0.0522 | 0.0462 |
| DEVIATIONS FRO M 3 LINES | 36 | 40.6801 | 1.1300 | |
| WITHIN GROUPS | 39 | 100.9322 | | |
| FITTING ONE LINE | 1 | 59.5777 | 59.5777 | 55.5085** |
| IMPROVEMENT OVER // LINES | 2 | 15.3750 | 7.6875 | 7.1625** |
| DEVIATIONS FROM // LINES | 38 | 40.7845 | 1.0733 | |
| TOTAL | 41 | 115.7347 | | |
| FITTING // LINES | 1 | 60.1477 | 60.1477 | 56.0400** |
| DEVIATIONS FROM // LINES | 38 | 40.7845 | 1.0733 | |
| BETWEEN GROUPS:- | | | | |
| PRE : POST+CONTROLS | 1 | 13.2795 | 13.2795 | 12.3726** |
| POST : CONTROLS | 1 | 1.5230 | 1.5230 | 1.4190 |
| TOTAL | 41 | 115.7347 | | |

**p<.01

TABLE 52

ANALYSES OF VARIANCE: FITTING WEIGHTED LINEAR REGRESSIONS OF THE RESPONSE LATENCY ON THE LOGARITHMIC FREQUENCY OF THE OBJECT NAME FOR SUBGROUP PE+OP BEFORE AND AFTER TREATMENT AND FOR THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | F |
|---|---|---|---|
| *For SUBGROUP PE+OP BEFORE TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 8.0070 | 7.8170* |
| DEVIATION FROM REGRESSION | 12 | 12.2815 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 20.2822 | |
| *For SUBGROUP PE+OP AFTER TREATMENT:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 6.3768 | 5.8449* |
| DEVIATION FROM REGRESSION | 12 | 13.0920 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 19.4688 | |
| *For CONTROLS:* | | | |
| DUE TO REGRESSION ON LOG. FREQUENCY | 1 | 46.8913 | 20.6079** |
| DEVIATION FROM REGRESSION | 12 | 27.3044 | |
| TOTAL VARIATION OF RESPONSE LATENCY | 13 | 74.1957 | |

* p .05
** p .01

TABLE 53

WEIGHTED LINEAR REGRESSION FOR SUBGROUP PE+OP AND CONTROLS

| SOURCE | REGRESSION |
|---|---|
| SUBGROUP PE+OP BEFORE TREATMENT | $y = -0.72 - 0.38x$ |
| SUBGROUP PE+OP AFTER TREATMENT | $y = -0.70 - 0.37x$ |
| CONTROLS | $y = -0.76 - 0.35x$ |

TABLE 54

ANALYSIS OF COVARIANCE: COMPARISONS OF WEIGHTED LINEAR REGRESSIONS FROM SUBGROUP PE+OP BEFORE TREATMENT, AFTER TREATMENT, AND FROM THE CONTROLS.

| SOURCE OF VARIATION | DF | SS | MS | F |
|---|---|---|---|---|
| FITTING THREE LINES | 3 | 61.2687 | 20.4229 | 13.9567** |
| DEVIATIONS FROM 3 LINES | 36 | 52.6780 | 1.4633 | |
| WITHIN GROUPS | 39 | 113.9467 | | |
| FITTING // LINES | 1 | 61.2121 | 61.2121 | 41.8315** |
| IMPROVEMENT OVER 3 LINES | 2 | 0.0566 | 0.0282 | 0.0193 |
| DEVIATIONS FROM 3 LINES | 36 | 52.6780 | 1.4633 | |
| WITHIN GROUPS | 39 | 113.9467 | | |
| FITTING ONE LINE | 1 | 60.2382 | 60.2382 | 43.4055** |
| IMPROVEMENT OVER // LINES | 2 | 33.0499 | 16.5250 | 11.9073** |
| DEVIATIONS FROM // LINES | 38 | 52.7347 | 1.3878 | |
| TOTAL | 41 | 146.0228 | | |
| FITTING // LINES | 1 | 61.2121 | 61.2121 | 44.1073** |
| DEVIATIONS FROM // LINES | 38 | 52.7347 | 1.3878 | |
| BETWEEN GROUPS:- | | | | |
| PRE : POST+ CONTROLS | 1 | 16.9228 | 16.9228 | 12.1940** |
| POST : CONTROLS | 1 | 15.1532 | 15.1532 | 10.9189** |
| TOTAL | 41 | 146.0228 | | |

**p<.01

TABLE 55

LINEAR REGRESSIONS FOR SUBGROUP PA

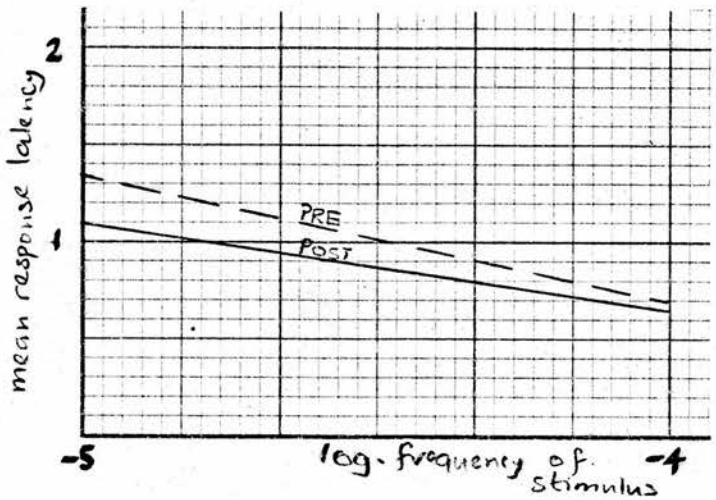



FIGURE 24

LINEAR REGRESSIONS FOR SUBGROUP PE

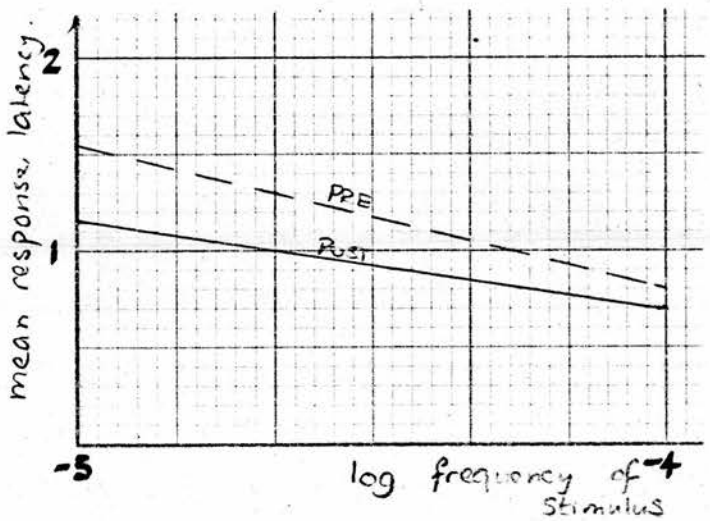



FIGURE 25

LINEAR REGRESSIONS FOR SUBGROUP PA+OP

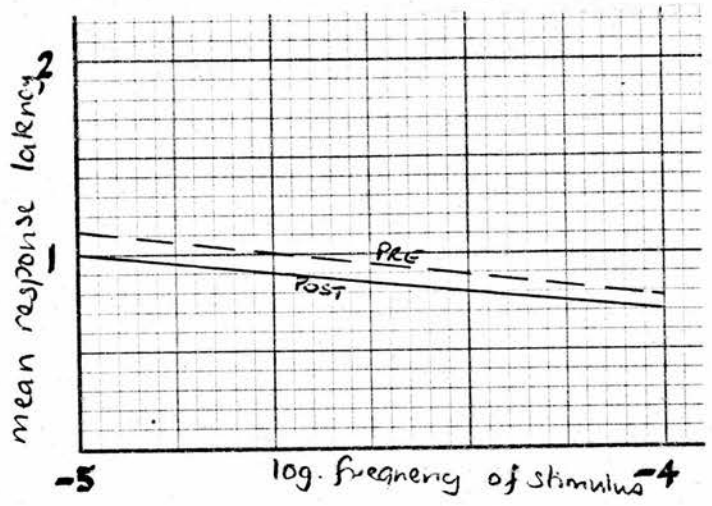



FIGURE 26

LINEAR REGRESSION FOR SUBGROUP PE+OP

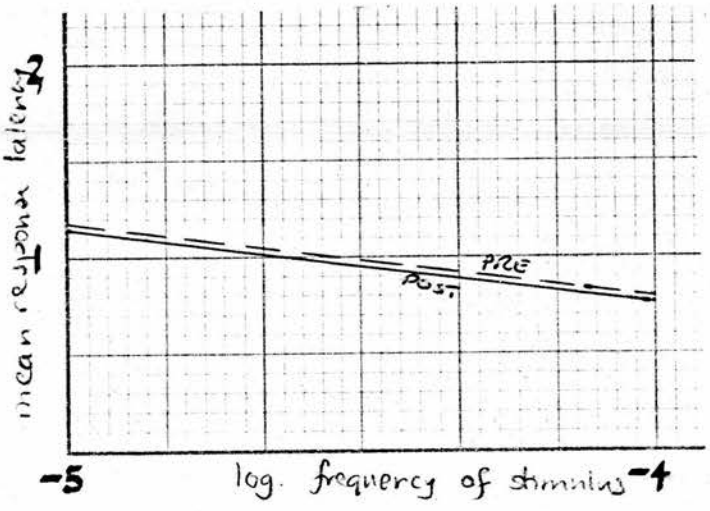



FIGURE 27

latency is observed - a reduction of sufficient magnitude to render the performance of these subgroups comparable with that of the controls.

Subgroup PE+OP unfortunately did not similarly benefit from treatment (TABLE 55). A significant difference was found between the intercept of the controls and this subgroup after treatment (and a significant difference was also found between this subgroup's before treatment intercept and its after treatment intercept plus that of the controls). As can be seen from the regression equations (TABLE 54 and from FIGURE 27 , before treatment, subgroup PE+OP was far slower than the controls and that L-dopa treatment hardly affected their level of performance.

## CONSIDERATION OF PSYCHOLOGICAL FACTORS

The results from the analyses of success scores, of the relative proportions of the type of errors made, and of the degree of difficulty experienced by subjects throw an interesting light on another aspect of performance. Confrontation naming is not a simple task; even the crudest model of confrontation naming needs recourse to a number of psychological functions/constructs such as perception, cognition, and memory.

The performance of the patients in comparison with the performance of the controls suggests no disturbance of

higher mental processes. Vocabulary is generally accepted as a good indication of intellectual ability. The Object Naming Test, a carefully selected set of graded vocabulary items, revealed no differences in the number of items correctly named by the untreated patients and by the controls. This finding is supported by a second finding, that the patients and controls experienced comparable degrees of difficulty with the rarer test-items. Furthermore, the analyses of the relative proportions of types of error do not support an alternative hypothesis of *specific* disturbance. A predominance of misidentification errors would be expected if the patients had perceptual or cognitive disturbances and a predominance of misnaming errors if the patients had some type of memory disturbance. No differences in the relative proportions of the types of error were found either between the untreated patient subgroups, or between the patients and the controls. Parkinsonian lesions thus appear to have little effect on the complex psychological functions involved in a confrontation naming task.

Treatment with L-dopa appears to have had neither a beneficial nor an adverse effect on psychological functions. After treatment the patients were able to name as many items correctly as were the controls, and there was no apparent difference in the degree of difficulty the subjects experienced on the rarer test-items. Furthermore, after treatment no measurable difference in the relative proportions of the types of error made by patients and

controls were observed. To confirm that L-dopa has little relevance for the complex psychological functions that subserve a confrontation naming task, a small battery of standard psychological tests was given to the patients before and after treatment.

## SPAN OF APPREHENSION: W.A.I.S. DIGIT SPAN SUBTEST

Before treatment, the mean digit span for the group as a whole was $10.55 \pm 2.4$. The mean digit span for the subgroups are contained in TABLE 56A. As would be expected from these means, digit span did not vary significantly with subgroup (TABLE 56B).

Similar results were obtained from the after treatment data. The group as a whole was found to have a mean digit span of $11.40 \pm 3.1$. As can be seen from TABLE 56A, the four subgroup means ranged from $11.20 \pm 2.70$ (for subgroup PE ) to $9.17 \pm 1.32$ (for subgroup PE+OP). No significant variation in digit span with subgroup was found (TABLE 56C).

On comparing before and after treatment performance, no significant difference was found for the group as a whole. Similarly, no significant change in performance was detected for any of the four subgroups (TABLE 56A).

In the above analyses 'scaled scores' were used in preference to raw scores. Digit span varies with age. Since a significant variation in age was found amongst the four subgroups (see Chapter 5), scaled scores which are corrected for age allow for meaningful intergroup

SPAN OF APPREHENSION

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 11.000 | 2.5690 | 12.091 | 3.7001 | 10 | -1.6360 |
| PE | 11.200 | 2.6998 | 11.300 | 2.2136 | 9 | -0.2308 |
| PA+OP | 10.000 | 2.0000 | 12.833 | 2.9944 | 5 | -1.9578 |
| PE+OP | 9.167 | 1.3292 | 8.833 | 2.0412 | 5 | 0.3952 |
| GROUP | 10.545 | 2.3729 | 11.394 | 3.0816 | 32 | -2.0096 |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.3620 | 1 | 0.3620 | 0.0654 |
| SURGERY | 17.4556 | 1 | 17.4556 | 3.1553 |
| INTERACTION | 1.9309 | 1 | 1.9309 | 0.3490 |
| ERROR | 160.4333 | 29 | 5.5322 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 32.2464 | 1 | 32.2464 | 3.7910 |
| SURGERY | 5.9264 | 1 | 5.9264 | 0.6967 |
| INTERACTION | 19.0302 | 1 | 19.0302 | 2.2372 |
| ERROR | 246.6759 | 29 | | |

TABLE 56

comparisons. The scaled scores are based on a large standardization population. Consequently, scaled scores permit a direct comparison of performance of the patients with the performance of the standardization or 'reference' population. The mean scaled score for the standardization population is 10±3. The mean scaled scores for the group as a whole and for each of the subgroups both before and after treatment compares favourably with the reference mean. The patients' means all lie well within one standard deviation of the reference mean.

IMMEDIATE RECALL FOR STORIES

Before treatment, the group as a whole scored 6.5081±3.2476 on the "immediate" recall of stories test. The means for the four subgroups are presented in TABLE 57A. Analysis of variance revealed that the amount of material recalled varied neither with type of Parkinsonism nor with surgical history. (See TABLE 57B).

After treatment, the group as a whole scored, on average, 6.772±3.2348 on the test. TABLE 57A contains the four subgroup means. As can be seen from TABLE 57C, the amount of material recalled after treatment did not vary with type of Parkinsonism or with surgical history.

On comparing the amount of material recalled under the before and after treatment conditions, no significant findings were obtained. The group as a whole and each of the four subgroups showed no significant change at all. (See TABLE 57A).

## IMMEDIATE RECALL OF STORIES

### A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 6.6429 | 3.6116 | 7.3750 | 3.3523 | 13 | -0.9371 |
| PE | 4.8571 | 2.3711 | 5.7143 | 3.7233 | 6 | -1.0406 |
| PA+OP | 7.2000 | 2.5824 | 6.8500 | 2.2611 | 4 | 1.3124 |
| PE+OP | 7.7500 | 3.7417 | 6.5000 | 3.5663 | 4 | 1.1937 |
| GROUP | 6.5081 | 3.2476 | 6.7742 | 3.2348 | 30 | -0.5556 |

### B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 3.8870 | 1 | 3.8870 | 0.3670 |
| SURGERY | 13.8019 | 1 | 13.8019 | 1.3031 |
| INTERACTION | 11.7502 | 1 | 11.7502 | 1.1094 |
| ERROR | 285.9787 | 27 | 10.5918 | |

### C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 10.5060 | 1 | 10.5060 | 0.9437 |
| SURGERY | 0.1453 | 1 | 0.1453 | 0.0131 |
| INTERACTION | 2.6707 | 1 | 2.6707 | 0.2399 |
| ERROR | 300.5974 | 27 | 11.1332 | |

TABLE 57

DELAYED RECALL FOR STORIES

The group of patients as a whole scored, on average, 5.2333±-3.4010 before treatment on the delayed recall for stories test. The subgroups' mean scores are presented in TABLE 58A. After treatment, the group's mean score was 5.0750±3.3017. The after treatment subgroup means are also presented in TABLE 58A.

Analysis of variance revealed that both before (see TABLE 56B) and after (see TABLE 58C) treatment the amount of material recalled after an hour's delay did not vary with either type of Parkinsonism or with surgical history. When the patients' before and after treatment scores were compared no significant difference was found. Similarly, no significant differences were found for any of the subgroups. (See TABLE 58A).

VISUO-MOTOR TASK: W.A.I.S. BLOCK DESIGN SUBTEST.

The group as a whole scored, on average, 8.949±2.5335 on the W. A.I.S. Block Design Subtest before treatment began. After treatment, their mean score was 9.1795±2.7613. The before and after treatment means for the four subgroups are contained in TABLE 59A. On comparing the patients' before and after treatment scores, no significant changes were found for the group as a whole, or for any of the subgroups. (See TABLE 59A).

Analysis of variance before treatment revealed no significant variation in scores on the test with either

## DELAYED RECALL OF STORIES

### A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 5.5357 | 3.6557 | 5.3929 | 3.1297 | 13 | 0.3513 |
| PE | 5.2500 | 2.7951 | 5.6250 | 3.3270 | 5 | -0.2713 |
| PA+OP | 4.8000 | 1.8825 | 4.4000 | 1.6451 | 4 | 1.0368 |
| PE+OP | 4.8000 | 5.1308 | 4.2000 | 5.3221 | 4 | 0.4848 |
| GROUP | 5.2333 | 3.4010 | 5.0750 | 3.3017 | 29 | 0.2501 |

### B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.6131 | 1 | 0.6131 | 0.0480 |
| SURGERY | 2.8167 | 1 | 2.8167 | 0.2204 |
| INTERACTION | 0.2297 | 1 | 0.2297 | 0.0180 |
| ERROR | 332.2697 | 26 | 12.7796 | |

### C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.1659 | 1 | 0.1659 | 0.0141 |
| SURGERY | 9.009 | 1 | 9.009 | 0.7635 |
| INTERACTION | 0.1604 | 1 | 0.1604 | 0.0136 |
| ERROR | 306.8081 | 26 | 11.8003 | |

TABLE 58

BLOCK DESIGN

A. COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

| | PRE | | POST | | DF | T |
|---|---|---|---|---|---|---|
| | MEAN | STD DEV. | MEAN | STD.DEV. | | |
| PA | 9.5000 | 3.1295 | 9.7220 | 3.5114 | 17 | -0.4320 |
| PE | 9.0000 | 1.5000 | 8.8890 | 2.0883 | 8 | 0.4843 |
| PA+OP | 7.8300 | 1.7224 | 8.0000 | 1.6733 | 5 | -0.4014 |
| PE+OP | 8.3300 | 2.4221 | 9.1667 | 1.8348 | 5 | -0.8333 |
| GROUP | 8.9490 | 2.5335 | 9.1795 | 2.7613 | 38 | -0.2635 |

B. ANALYSIS OF VARIANCE BEFORE TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 1.1308 | 1 | 1.1308 | 0.1731 |
| SURGERY | 12.9808 | 1 | 12.9808 | 1.9869 |
| INTERACTION | 1.1192 | 1 | 1.1192 | 0.1713 |
| ERROR | 228.6666 | 35 | 6.5333 | |

C. ANALYSIS OF VARIANCE AFTER TREATMENT

| SOURCE | SS | DF | MS | F |
|---|---|---|---|---|
| TYPE | 0.7853 | 1 | 0.7853 | 0.0998 |
| SURGERY | 6.1603 | 1 | 6.1603 | 0.7831 |
| INTERACTION | 7.4647 | 1 | 7.4642 | 0.9489 |
| ERROR | 275.3332 | 35 | 7.8667 | |

TABLE 59

type of Parkinsonism or with surgical history. (See TABLE 59B). Similar findings were obtained from the after treatment scores. (See TABLE 59C).

As explained in Chapter 5, age-corrected or "scaled" scores were used in preference to "raw" scores on this test. The mean for "scaled" scores is 10±3. All the means obtained for the patients both before and after treatment compare favourably with this "scaled" mean. There thus appears to be no indication that there is a deficit in the patients' performance on this task either before or after treatment.

How do the present findings on Parkinsonism, L-dopa, and psychological functions compare with previous work in this area? Unfortunately few clear and simple answers are to be found.

The two studies in which the performance of Parkinsonian patients and matched controls were compared are clearly contradictory. Marsh et al. (1971) found that (untreated) Parkinsonian patients consistently scored less than controls on tests of auditory and visual perception, auditory and visual short-term memory, verbal learning (an 'intermediate' memory task), attention and concentration. However, Donnelly et al. (1973) found no significant differences in performance levels of (untreated) Parkinsonian patients and controls on the W.A.I.S. and Wechsler Memory Test.

Even less clear is whether L-dopa treatment has an effect on psychological functions. Cotzias observed clinically (1969a) that the "mental effects" of L-dopa treatment included "enhanced interest" and "improved memory". Beneficial effects on "interest" or "attention" were experimentally found by Puca et al. (1971), and by Megna et al. (1971) but denied by Marsh et al. (1971). Significant improvement in memory had been confirmed by Vernet et al. (1973), and by Megna et al. (1971), but denied by Donnelly et al. (1973), and only partially confirmed (i.e. only for 'intermediate' but not for 'short-term' memory) by Marsh et al. (1971). Improvement in general intellectual functioning (as measured on the W.A.I.S.) was found by Beardsley et al. (1971), but not by Vernet et al. (1973), nor by Donnelly et al. (1973). Loranger et al. (1973) found a significant improvement on the W.A.I.S. in their group of patients on retest after one year. However, after 30 months of continuous treatment, this improvement was not maintained.

There is perhaps only one finding common to the present study and previous findings: L-dopa does not (at least in the short-term) *adversely* affect higher mental processes. Beyond this, clearly, there are contradictions which need to be accounted for. Riklan (1973) has criticised a wide spectrum of Parkinsonian literature for its less than rigorous methods of control, and Donnelly (1973) has emphasised the hazards of design that are always present in a test-retest experiment. The present

author is made uneasy by the tendency shown in the articles cited above for ignoring variables in subject selection. The present investigation has shown both type of Parkinsonism and surgical history to be important.

# CHAPTER 10

## EVALUATION, CONCLUSIONS AND REFLECTIONS

The act of speaking involves highly sophisticated sequences of a large number of muscle groups. Indeed, speaking is perhaps the most complex of motor activities performed by Man, yet its intricacy and delicate patterning are obscured by the very frequency and apparent effortlessness with which the activity is performed.

We cannot state exactly the number of muscles that are necessary for speech and that are active during speech. But if we consider that ordinarily the muscles of the thoracic and abdominal walls, the neck and face, the larynx, pharynx, and the oral cavity are all properly co-ordinated during the act of speaking, it becomes obvious that over 100 muscles must be controlled centrally. Since the passage from any one speech sound to another depends ultimately on differences in muscular adjustments, fourteen times per second an "order must be issued to every muscle," whether to contract, relax, or maintain its tonus....it is clear, however, that the readjustment does not occur simultaneously for all muscles, but that various groups of muscles have characteristic timing; some are active shortly before the acoustic onset of a phoneme, some during, and some shortly after. Thus we gather that the rate at which individual muscular events occur (throughout the speech apparatus) is of an order of magnitude of several hundred events every second. It is evident that the activation of so many muscles in such a short time span cannot depend on volition alone. There must be some automatisms - whole trains of events that are "preprogrammed" and run off automatically. Automatic sequences such as these are called *synergisms;* they form the basis of all motor phenomena in vertebrates. The physiology of speech production would be very simple if every phoneme were

associated with one and only one pattern of muscular interaction. However, this is not what we find. The muscular activity associated with one phoneme is influenced by the phonemes that precede and follow it. Thus the motor patterns...are complex motor configurations that extend over relatively long periods, as in the duration of a syllable or word.

The intricacy of the problem becomes apparent if we draw an analogy between the sequence of events during speech and in drumming with the fingers on a table top. Both proceed at a rapid rate, but when we drum out a melody with our fingers, it does not matter in which order each finger falls on the table. The easiest is to use a single order, letting the small finger always be the first and the index always the last. But in speech production the order of activation and precise timing is of paramount importance. (Lenneberg, 1967)

Clearly, even slight alteration in the motor system will be reflected in disturbed performance. Furthermore, the alteration may occur at any level of the system, from the more central control areas to the muscles at the periphery. For some time now, theoretical assumptions about dysarthria have ceased to arouse the heated controversy of former times: it is now appropriately recognized that under the rubric "dysarthria" many kinds of speech disturbance may be subsumed and that the disturbance may be consequent upon lesions located centrally and/or peripherally in the nervous system. Theory, however, is not always reflected in practice, and this is nowhere more apparent than in the area of Parkinsonian dysarthria.

With, perhaps, the exception of Leyser (1924), it has always been assumed that the speech disturbances in Parkinsonism are due to the rigid and tremulous state of the muscles concerned. Speech pathologists and neurologists alike have long considered the Parkinsonian dysarthria to be no more than a manifestation of the disturbed state of

the peripheral musculature. Those facts that are known, however, in no way support this popular assumption. Although in 1961 Canter demonstrated, contrary to expectation, that neither the degree of rigidity nor the degree of tremor correlated with the magnitude of the speech disturbance, the most damaging evidence has come from the field of neurosurgery. Repeatedly it was found that stereotactic intervention which successfully reduced tremor and rigidity did *not* have the predicted effect of lessening speech disturbances. Moreover, in a substantial number of patients who pre-operatively had had no trace of dysarthria, stereotactic intervention actually *induced* speech disturbances *while at the same time* successfully reducing rigidity and tremor.

It is indeed puzzling that so contradictory a state of affairs has persisted, and for so long. Perhaps the reluctance to up-date an outmoded hypothesis is indicative of the lack of concern with which dysarthria is still regarded. As it stands, the evidence to date not only overwhelmingly contradicts the popular assumption that Parkinsonian dysarthria is due to the dystonia of the periphery, but it also strongly suggests that, in rethinking the question, attention should be directed towards the central rather than the peripheral aspects of the motor system.

But what is to replace the clearly erroneous popular explanation of Parkinsonian dysarthria? Since two elements of the Parkinsonian motor triad - rigidity and

tremor - have been shown to bear little relevance to the dysarthria, akinesia may be seen as a possible alternative. Interestingly enough, in spite of the fact that over the past few years the re-definition of Parkinsonism as a dopamine-deficiency syndrome has precipitated an unprecedented wave of interest in akinesia, no-one has paid serious attention to the relationship between akinesia and Parkinsonian dysarthria.

The present investigation was designed to test precisely this relationship. In discussing the results from this investigation attention will be drawn to three aspects: an evaluation of the research hypotheses; the clinical implication of the research findings; and, finally, theoretical implications of the research findings.

## EVALUATION OF RESEARCH HYPOTHESES

HYPOTHESIS 1: *The lesions which cause akinesia are responsible for the speech disturbances of Parkinsonian patients.*

Of all the Parkinsonian symptoms, it is akinesia which is least understood. Kinnier Wilson is generally recognized as having introduced the term 'akinesia' to neurology, and in particular to the area of the subcortical disorders.

However, as de Ajuriaguerra (1971) pointed out, this was no neologism of Wilson's. Long before Wilson incorporated the term in his 1925 articles to the *Lancet*, Wernicke and some psychiatrists had used the term 'akinesia' in describing certain motionless aspects of catatonia.

Perusal of current neurology textbooks shows that although the term is widely used, over the intervening half century its scope of reference has become highly restricted. It will be remembered that Wilson postulated a dual motor system - a 'pyramidal' system which subserved 'voluntary' action, and an 'extra-pyramidal' system, centering around the subcortical muclei, that subserved more 'reflexive' (or, in Wilson's terminology, 'spontaneous') movement. 'Akinesia' is now conventionally used to refer to symptoms arising from damage to this 'extra-pyramidal' system, to a loss of automatic and of associated movements, and to those movements involved in the expression of emotion. Used in this way, it is difficult to conceive of any possible connection between akinesia and dysarthria. Reference to Wilson's own writing on the subject, however, clearly shows the current usage of the term to be based on a misconstruction.

Wilson used 'akinesia' in a manner that reflected the term's psychiatric origins. For him, 'akinesia' implied a decrease of spontaneous *as well as* 'voluntary' movement. It was due to a *central* lesion involving damage to the 'higher' control centres and resulting in "deprivation of, or serious reduction in, normal impulses to movement, both

of the voluntary and spontaneous kind" (Wilson, 1925). Behaviourally, akinesia was manifest in slowness and "poverty" of movement. The affected motor system appeared to Wilson to lack "spontaneity" and "drive", and the extremities themselves seemed "lazy" and required "constant coaxing to activity".

The picture of disturbance provided by this investigation clearly contains all the distinctive features of akinesia Wilson described in his articles. The two forms of motor behaviour studied (i.e., writing and speech) displayed similar disturbances. There was a substantial delay, in both modalities, before a motor sequence was initiated. This delay could not be related to 'preparation planning time' since two of the measurements were based on tasks involving well-practised sequences of activity (writing name and address, and reciting 'rote' speech sequences such as counting from one to ten and naming the letters of the alphabet). Moreover, as the confrontation naming task revealed, the delay in initiation was related to neither the difficulty of the task nor to the length of the required response sequence.

When movement did occur, it was seen to take longer than 'normal' for its elaboration and to be less precise in execution. Writing, for example, tended to be small, 'cramped' and not easily legible. All patients were required to write in pencil and their writing produced strikingly light or faint marks on the paper. The patients themselves were highly critical of their writing and

acutely aware of its inadequacy as a means of communication. A large proportion of the patients reported that they had so organized their life style that they no longer wrote anything at all. Speech revealed comparable disturbances. It was soft. Words were elongated and imprecise in articulation. Pauses and prosodic features were markedly reduced and in some cases even absent. The panel of judges considered the patients' speech not easily understandable and only moderately effective as a means of communication. Writing and speaking also showed disturbances in the regularity of rate of execution. In both modalities it was observed that the execution of a sequence began slowly (after an initial delay), and then rapidly accelerated ('festination'). This acceleration was sometimes followed by a prolonged pause ('freezing').

'Akinesia', according to Wilson, is clinically independent of, and not to be confused with, rigidity; "No constant relationship between the degree of peripheral rigidity and decrease of spontaneity of voluntary movement can be established, for the reason that the motor phenomena under discussion are frequently found where muscular rigidity is not a conspicuous feature" (Wilson, 1925). Denny Brown (1962) has convincingly demonstrated, in subhuman species, that lesions of the globus pallidus do produce akinesia unrelated to rigidity. Findings such as this, and clinical observation, have led him to take an unequivocal stand regarding the nature and significance of

akinesia. For Denny Brown, akinesia and not tremor or rigidity, is the 'true' symptom of damage to the subcortex. Perhaps the most compelling evidence of the independence of rigidity and akinesia is to be found in the literature reporting the results of stereotactic surgery for the reduction of rigidity (and of tremor). Selby (1967), for example, found that although in a high proportion of cases rigidity (and tremor ) is alleviated by stereotactic placement of additional lesions in the subcortical ganglia, akinesia is not similarly benefited. This is not an isolated observation. Schwab et al. (1959) found that akinesia may persist, or even *increase* after pallidectomy, and Fager (1968) found that akinesia may be produced by the very surgical lesions that reduce rigidity (and tremor).

In the present study, although all patients had at least some degree of akinesia, twenty nine per cent of the group had no rigidity at all (eighteen per cent had 'slight' rigidity, forty one per cent 'moderate' rigidity and twelve per cent 'marked' rigidity). As has already been said, *all* patients in the study had some degree of akinesia. Only five per cent had a 'slight' degree of akinesia, twenty seven had 'moderate' akinesia, and sixty eight per cent had a 'marked' degree of akinesia. When the speech recordings of these patients were played to the panel of judges for evaluation, only two patients (five per cent) were found to have no impairment at all on all five scales. Clearly within this group there was a sizeable

number of patients without rigidity but with akinesia and speech disturbances. Moreover, only those two patients with 'slight' akinesia (one with marked rigidity, the other with moderate rigidity) were found to have 'normal' speech.

Leading on from this last point, a final question, arising from the first experimental hypothesis, needs to be considered. Does the degree of speech disturbance vary with the extent of subcortical damage, and hence the degree of akinesia? The experimental evidence suggests that this does appear to be the case. The experimental group was such that although it comprised paralysis agitans patients (with the more circumscribed lesion/s) and post-encephalitic Parkinsonian patients (with more extensive, and possibly more disseminated lesions), both types of Parkinsonism were found to be associated with comparable degrees of akinesia. Nevertheless, three of the experimental tasks revealed that the degree of disturbance to complex motor sequences varied significantly with type of Parkinsonism. Paralysis agitans patients (irrespective of surgical history) were found to be able to begin writing their name and address sooner than post-encephalitic patients; and paralysis agitans patients were considered by the judges to speak more intelligibly and with less dysarthria than post-encephalitic patients.

A significant difference in the degree of akinesia was found between patients who had and those who had not previously undergone stereotactic surgery. Patients with

a surgical history were found to be significantly more clinically akinetic than their unoperated counterparts. On four experimental tasks unoperated patients were found to perform significantly better than operated patients: size of writing, time taken to write, intelligibility of speech, and degree of dysarthria.

In brief, therefore, the evidence in support of the first hypothesis is threefold. First, and perhaps most importantly, the nature of the disturbances observed complies fully with the listing of the distinctive features of akinetic disturbance as described by Wilson, who introduced the term. Secondly, the incidence of speech disturbance in the experimental group overlaps more closely with the incidence of akinesia than with the incidence of rigidity. And finally, there does appear to be some evidence to suggest that the degree of disturbance to complex motor sequences such as writing and speaking varies with the degree of akinesia.

HYPOTHESIS II: *The lesions which occasion the speech disturbance are biochemically mediated.*

De Ajuriaguerra (1971), in an attempt to economically define akinesia suggested that "akinesia is what L-dopa modifies". Although this is a circular definition, it does concisely summarise the current view of L-dopa and akinesia (see Chapter 3). If the basic hypothesis of this investigation were correct, i.e. that the speech disturbances in

Parkinsonism are *akinetic*, one would expect with L-dopa treatment similar modifications both of the clinical aspects of akinesia and the measures of speech disturbance. The experimental results from this investigation provide overwhelming support for this hypothesis. All patients in the study showed at least some evidence of clinical improvement, and it has been shown throughout the preceding chapters of results, that the group as a whole were found to have significantly less disturbed speech after L-dopa treatment had reached maximum levels than before treatment had commenced. With treatment, the speech of the patients was judged to be more intelligible, less dysarthric, to contain more prosodic features, and to show less phonic disturbance. Furthermore, their speech was shown to be louder, and less monotonous. They were able to sustain phonations for far longer than they had prior to treatment. Their reading was more fluent and faster and they were able to start speaking with 'normal' minimum delay. On only one dimension of speech disturbance - festination - was no improvement seen. Both the judges' ratings, and the analysis of regularity in counting showed that festination was not altered by L-dopa treatment.

Improvement in complex motor sequences was also found in the other modality studied. After treatment, patients were able to start writing sooner, to write larger and more legibly than they had before treatment had begun.

All these changes in performance were at least at the 5% level of confidence.

When the four subgroups are considered separately, it is seen that each responded differently to treatment. TABLE 60 summarizes the changes in performance on all the

SUMMARY OF CHANGES WITH TREATMENT

| PARAMETER | SUBGROUP | | | | GROUP AS A WHOLE |
|---|---|---|---|---|---|
| | PA | PE | PA+OP | PE+OP | |
| SPEECH PARAMETERS | | | | | |
| mean voice volume | I | I | - | - | I |
| variation in volume | - | - | - | - | I |
| sustained phonation | I | I | I | I | I |
| rate of reading | B | I | B | I | I |
| phonation/pause ratio | I | W | W | W | - |
| regularity of speech | - | - | - | - | - |
| initiation of automatic speech | I | - | I | - | I |
| mean response latency | I | I | I | W | I |
| WRITING PARAMETERS | | | | | |
| initiation of writing | I | I | - | - | I |
| size of writing | I | I | B | B | I |
| time of writing | - | - | - | - | - |
| RATINGS OF SPEECH | | | | | |
| 'INTELLIGIBILITY' | I | I | - | - | I |
| 'DYSARTHRIA' | I | I | - | - | I |
| 'PROSODY' | I | - | - | - | I |
| 'FESTINATION' | - | - | - | W | - |
| 'PHONIC' | I | I | - | - | I |

KEY:
I = significant improvement.
B = improvement, but not at the 5% level.
W = significant deterioration.
- = no measurable change.

TABLE 60

test times for each subgroup. As can be seen from the table, subgroup PA showed a significant improvement on eleven items, improvement (but not significant) on one item, and no deterioration at all. Thus on fifteen items, subgroup PA

improved on twelve. Subgroup PE improved significantly on nine items, but was worse with treatment on one item: phonation/pause ratio. Subgroup PA+OP improved significantly on only three items, showed some improvement on another two and was seen to be adversely affected by treatment on the phonation/pause ratio item. Subgroup PE+OP improved on only two items. In addition, this subgroup showed improvement, but not significant, on the size of writing, and a significant deterioration on three items: festination, phonation/pause ratio and mean response latency.

The differences in modification of speech disturbances in response to treatment are clearly related both to type of Parkinsonism and to surgical history.

The differences are also related to the ratings of degree of akinesia, and to the amount of clinical improvement. Before treatment had commenced, operated patients were found, on clinical criteria, to be significantly more akinetic than unoperated patients. Once treatment had reached an optimal level, it was found that both operated and unoperated patients showed similar degrees of clinical improvement. From this it may be inferred, that despite the fact that both groups improved with treatment (i.e., as far as clinical criteria are concerned), the relative differences between them remained - unoperated patients were less akinetic than operated patients both before and after treatment. Type of Parkinsonism was also shown to be important. Before treatment had commenced there was no significant difference in the degree of akinesia shown by

paralysis agitans and post-encephalitic patients. However, on clinical criteria, paralysis agitans patients were found to benefit significantly more than post-encephalitic patients from L-dopa treatment.

The difference between subgroups, however, are not related to the L-dopa dose level. As demonstrated in Chapter 5, similar maximum dose levels were empirically established for each subgroup.

There were a number of parameters investigated that, as expected, showed no apparent deficit. Neither before nor after treatment were the patients found to be less successful than normals in correctly naming the objects in the confrontation naming task. Furthermore, when the patients did make errors on this task, the type of errors were similar to the type of errors the controls made. Again, the type of errors made by the patients was not influenced by L-dopa treatment.

The results from the small battery of psychological tests confirmed the impression formed from the patients' performance on the confrontation naming test.

The patients were average on the two W.A.I.S. subtests- 'Digit Span' and 'Block Design'. Furthermore L-dopa treatment had no measurable effect on performance on these two tasks. L-dopa treatment also did not affect the patients' ability to recall verbal material. Recall tested immediately and after an hour's delay was neither enhanced nor reduced by treatment.

## GENERAL CONCLUSIONS

The present investigation has yielded unambiguous support for the basic experimental hypotheses. There seems little to contradict the hypotheses that the speech (and writing) disturbances are akinetic in nature; that the degree of disturbance to both speech and writing varied according to the degree of akinesia; that the degree of all these disturbances is closely related to both type of Parkinsonism and surgical history, i.e. to differing degrees of subcortical involvement; that these disturbances are ameliorated by L-dopa treatment; and that the degree of amelioration is related to both type of Parkinsonism and surgical history, i.e. the degree of subcortical involvement.

## CLINICAL IMPLICATIONS OF THE RESEARCH FINDINGS

Although the present investigation was primarily concerned with the nature of the speech disturbances consequent upon subcortical lesions, the results do also have practical, clinical relevance.

The results of this investigation have shown that

L-dopa treatment is associated with a reduction of not only the clinical aspect of akinesia, but also with a reduction of the disturbances to speech and to writing. This is an extremely important finding. No other anti-Parkinsonian treatment has been shown to *benefit* speech. Surgery was found to be associated with an increased disturbance to speech. In some cases, surgery was found to actually *induce* speech disturbances (see Chapter 4). Anti-cholinergic drugs apparently neither exacerbate nor ameliorate speech disturbances (Schawb et al., 1959).

The investigation was 'short-term'. The patients were retested a few days after they had been stabilized on their maximum dose levels. That improvement to speech and writing is seen on retest suggests a) that the changes observed are an immediate response to treatment, and, b) that in order to obtain this effect, no more medication is required than that which is needed to ameliorate the clinical picture of akinesia.

Despite the fact that the immediate effect of treatment is encouraging, it is not possible to predict with confidence the long-term effects. It would be naïve to expect that altering part of the amine chemistry of the brain in either the short or the long term would have no effect on other aspects of neurochemistry. As yet, our knowledge of this area if not sufficiently advanced to predict the possible effects of continued treatment. Furthermore, the disease process is itself progressive. Whether increasing degeneration will continue to be

counteracted by this form of treatment is by no means clear. Long term studies are urgently needed.

The results of the present investigation have some relevance to future studies. It has been demonstrated that both type of Parkinsonism and surgical history are important variables. Both before and after treatment, differences between the four subgroups were observed on a number of parameters. In Chapter 7, for example, it was shown that not only did the severity of speech disturbances vary with subgroup, but also that there were differences in the pattern of the disturbances shown by the subgroups. Moreover, throughout the investigation results have been obtained that strongly indicate that response to treatment varies with type of Parkinsonism and with surgical history. Clearly, future studies cannot ignore these variables. One can no longer assume that a homogeneous population is subsumed under the rubric 'Parkinsonism'.

The patient population studies included patients who had and those who had not previously undergone stereotactic surgery. The design of the investigation was such that the performance of operated and unoperated patients, irrespective of type of Parkinsonism, could be compared both before and after treatment. The results from these analyses have direct clinical importance since apart from a long term reassessment on clinical criteria by Gillingham (1969), the present writer has been unable to find any study which provides evidence of a long term

follow-up of speech disturbances following surgery. Three important conclusions may be drawn from these results:

1. The beneficial effects that stereotactic subcortical surgery affords in reducing tremor and/or rigidity do not last as long as ten years. No significant difference in degree of tremor and/or rigidity could be found between operated and unoperated patients in this study.
2. The unwanted effects of stereotactic surgery, i.e., increased akinesia and speech and writing disturbances do, unfortunately, last as long as ten years.
3. Previous stereotactic subcortical surgery limits the degree of improvement with L-dopa. Patients who had undergone surgery showed less amelioration of speech and writing disturbances as well as less reduction in the clinical signs of akinesia than their unoperated counterparts.

Clearly the behavioural consequences of subcortical surgery are serious. Indeed, these results throw doubt upon whether, ever again, surgery can be offered with confidence and compassion as a method of treatment for Parkinsonism. Further long term studies on this particular implication of the present investigation are urgently needed.

The control function for a sequence of movements such as speech is very complex indeed. This was made most apparent in the rather lengthy quotation from Lenneberg at the beginning of this chapter. To postulate a single level, single type of control system to account for the extremely complex, delicately timed, highly organized segments of motor sequences that are patterned to form, for example, speech or writing, would be to grossly over-simplify the nature of the system. Clearly what is required is not a unitary control system, but rather a complex function elaborated at a variety of levels, and comprising a variety of types or forms of control. However, this investigation relates to only a specific domain of this control system. We are concerned here not with the quality of the movement sequence, i.e., for example, the quality of the articulation of discrete words, or the syntactic structure of utterances. What we are concerned with is the timing or the regulation of the numerous motor events that comprise the speech or writing sequence. The central issue of this investigation revolves around the temporal aspects of performance.

The temporal regulation of behaviour with which we are concerned is non-specific. It is necessary for any kind of motor sequence - walking, writing, speaking, playing the piano or cricket, and so on. The present

investigation has confirmed that both speech and writing are similarly affected in Parkinsonism, and once L-dopa treatment has reached an optimal level and clinical improvement, similar changes in both modalities may be seen. The control for motor sequences must therefore be *centrally* located.

Movement has three discernible parts; an initiation, a description, and a cessation. For its part, the nervous system initiates and 'drives' the movement, it collates information fed back through sensory and proprioceptive pathways and, on the basis of this, guides the movement through its description. Finally, at the appropriate time, the nervous system ends the movement. However, as Walshe pointed out (1948), the pyramidal system, although usually accredited with the elaboration of "voluntary" movement, is itself incapable of exerting this central control alone. Instead, the 'pyramidal' system functions in concert with the 'extra-pyramidal' system and it is far more plausible to ascribe the control function to this latter part of the nervous system. Indeed, this older part of the system appears more than adequately provided to act as a central control centre. It consists of a number of nuclear masses interconnected with each other and, through complex efferent pathways, with diverse and important neural centres. It is reciprocally connected with the very cells of the motor cortex that give rise to the 'pyramidal' system, with the main sensory relay station (the thalamus), and with the

ascending reticular formation. It also exerts some influence on the γ-motoneurones of the periphery through its (albeit small) rubrospinal tract. The multisynaptic nature of this system, its diverse connections and many 'looping' pathways establish it as the physiological servosystem at the centre of the nervous system and enable it to exert intimate control through all three stages of all types of movement.

The type of model that seems most appropriate to describe how control of behaviour is normally elaborated is a synchronous one. Lashley (1951) argued most strenuously in favour of this type of control. More recently, Lenneberg (1967) has dealt at length with this topic, and after evaluating research findings from a variety of areas, has given his support to a synchronous model to describe the control function.

This model makes two important assumptions. The first assumption is that there is a central time-keeping mechanism that synchronizes the activity of subsystems or "synergisms" in Lenneberg's terminology. The control clock emits signals or pulses and the subsystems synchronize their activity with the rate of the central clock. This type of model is often likened to the manner in which a busy railway station functions. Trains enter and depart from the station according to the preplanned times, laid down in the timetable, and each train observes time according to the station clock. The second assumption is that, under normal conditions, the clock runs at a

reasonable frequency. The periodicity of the clock can be deduced, for example, from the rate of utterance obtained in the present investigation - the periodicity of the clock for speech appears to be 87 words per minute. The clock may be "overridden". One can talk faster or slower. Interestingly, however, this overriding results in a less stable rate of output. One can talk faster, but it is not with ease that one can talk faster for a prolonged period. Without concentration, the speed of utterance tends to rectify, and talking at the normal rate usually soon occurs. Furthermore, it seems that the clock may be overridden only in a crude fashion. It is only with considerable concentration that one can speak at, say, twice the normal rate of utterance.

Damage to this central clock would clearly produce disorganized, free-wheeling behaviour. One would expect difficulty in co-ordinating subsystems and this would be manifest in erratic performance. Starting and stopping activity would be difficult, since there would be nothing for the numerous subsystems to pace themselves by. A marked delay *was* observed in the initiation of both writing and speaking in the (untreated) Parkinsonian patients. The delay, however, was shown by the confrontation naming test to be *constant* for a number of different words. This finding clearly is not consonant with the assumption of a disordered central clock, since *random* time changes would be expected.

That the present results are not as one would predict

by a disturbance to a central clock does not in any way throw doubt on whether such a mechanism can be held to describe normal function. What has been observed in this investigation is not simple evidence that a central clock is disrupted. This statement needs amplification.

It has long been the tradition to observe the disturbance of function in patients with clearly located neurological lesions in an attempt to understand more fully the relationship between brain and behaviour. It has been a tradition that has required much care and awareness from the investigator lest he fall into any of the logical pitfalls that litter the past history of this area of enquiry. A number of the difficulties facing the investigator centre around the essentially inferential nature of the method of enquiry. The nervous system is almost entirely inaccessible to direct observation. The exceptions to this are trifling: the termination of one nerve, the optic, can be seen, and, according to Gowers (1886-1888), "some of the nerve-trunks in the limbs can be felt, either in the normal state or when enlarged by disease". As a rule, the state of the nervous system can be inferred only by the manner in which its work is done - and this only with difficulty. Other difficulties concern the nature of the disturbance in behaviour. It has long been believed that any performance could be lost or impaired, and that the type of defect produced depended on the location of the lesion. The relationship between

disturbance to performance and location of the lesion, however, is not quite so simple nor quite so transparent. Kurt Goldstein, working in the field of asphasia, considered this very problem. In his book, *Language and Language Disturbance* (1949), he poses the question:"...we are first of all confronted with the general theoretical problem of whether and how far we are justified in assuming such a relationship of simple causality between lesion and symptom/s : *Are symptoms, i.e.,* modifications of behaviour, the direct expression of a definite disturbance of function, or are there other factors involved which at least contribute to the production of symptoms?" Later in his book, after reviewing the literature, Goldstein makes his conclusion quite clear:

> The survey regarding the factors determining the configuration of symptoms in brain damage has shown that symptoms are only partly the direct results of the damage. It has further become evident that, to a greater or lesser degree, the symptoms are an expression of the organism's struggle with the defect in its attempt to adjust itself in spite of some interference by the defect. The symptoms become understandable only from the organismic point of view....."

Although the name of Goldstein is most frequently associated with this particular point of view, he is not alone. Henry Head, for example, also emphasised the essential functional plasticity of the nervous system:

> The various disorders of speech produced by injuries of the brain manifest in the ways in which the organism masters a situation, demanding the use of language, with a defective mechanism. A certain form of behaviour becomes necessary as a sequel to certain external or internal events: some normal facility is disturbed by the presence of the lesion and the orderly exercise of a series of functions suffers in consequence. A new attitude must be

assumed; for the patient has to face a familiar situation with an imperfect apparatus. It is as if he were compelled to play lawn tennis with a broken racquet; many of his favourite strokes will become impossible and he will have to vary his conduct in accordance with the defective instrument in his hand.

The movements he adopts in consequence of these unusual conditions do not form integral parts of his normal method of playing the game. A man who has a pain in his toe walks differently from one whose heel is affected. *But neither gait reveals the elements out of which normal walking is composed.*

There are a number of control models that can be advanced as alternatives to the central clock model. The model that appears most appropriate to the results of this investigation is an asynchronous control model. This type of model does not assume a central time-keeping mechanism (hence its name). Instead, this model is based on the assumption that the various subsystems pace themselves by signalling to each other that an event is just about to happen, or that an event has just occured. These inter-subsystem signals are usually alikened to "handshakes" between subsystems. Coherence and synchrony of this type of model clearly depend upon these inter-subsystem signals.

An asynchronous model is readily translatable in terms of the known neurology of the subcortex. There is overwhelming evidence that a decrease in striatal dopamine is an almost invariable factor in the production of the Parkinsonian syndrome. The literature on this subject has been dealt with in Chapter 3. Let it suffice to merely point out here that dopamine applied microelectrophoretically

leads to inhibition in many neurones in the caudate nucleus (Bloom et al., 1965). Mettler (1945) has shown, in apes, that bilateral lesions of the caudate nucleus produce over-activity, or hyperkinesis. The principal outflow from the striatum is to the pallidum which lies in the efferent pathway, from the thalamus, for movement. According to Mettler (1967) the striatum normally functions to inhibit these thalamopallidal circuits. Experimental evidence supports this claim. Purpura et al. (1967) for example have shown that stimulation of the caudate inhibits the outflow of impulses from the pallidum. Interestingly, and highly relevant here, are studies by Van Buren (1963) demonstrating the behavioural consequences of such stimulation. During subcortical stereotactic surgery on Parkinsonian patients, they stimulated the head of the caudate nucleus and found this induced a "basic disturbance in which the impulse to speak or to continue another task has been dulled or forgotten".

All these studies suggest that the integrity of the striatum is crucial for inter-subsystem transmissions. Damage to the striatum results in a diminution of its inhibitory influence on the spontaneous activity of pallidalthalamic circuits. Under these conditions, inter-subsystem transmission would clearly be extremely difficult. The signal-to-noise ratio of any "signalling" would be poor. Prolonged bombardment of signals may be necessary in order to be "perceived" by the receiving subsystem or subsystems.

This type of model accounts for the delayed initiation of motor sequences, and for the changes observed within the sequence - the elongated words separated by shortened pauses. It explains why the judges considered the speech of patients as being imprecisely articulated. It also explains the reduction of prosodic features, since many of these are temporal suprasegmental patterns. This type of model can also account for the changes observed following L-dopa treatment. L-dopa treatment, in restoring striatal dopamine would enable striatal inhibition to be re-established. The behavioural consequences of this can readily be deduced since the signal-to-noise ratio of the system would be increased, and inter-subsystem transmission facilitated.

This type of model, however, does not account for festination. Interestingly, L-dopa treatment did not have an appreciable effect on festination when all the patients are considered together. However, the judges' ratings of festination suggest that, with treatment, PE+OP were significantly more festinant. This type of model also does not account for the divergent results from the word-pause ratio analyses. With treatment, subgroup PA, the subgroup with the least subcortical damage, perform qualitatively differently from the three other subgroups, all of which had greater subcortical involvement.

There is one particular study reported in the literature that has relevance here. Guiot et al. (1961) found that on stimulating the ventrolateral (VL) thalamic

nucleus they were able to disrupt speech. They either slowed down or accelerated their patients' counting. These results suggest disturbance to the ventrolateral nucleus fundamentally disrupts a central clock mechanism. That the VL was a favoured site for stereotactic surgery, and that this results both in increased akinesia (Fager,1968), and in increased speech disturbances (see Chapter 4) provides additional support for the view that the VL nucleus, which has also been a favoured surgical target, are intimately bound up with the central regulation of performance.

The Guiot results suggest that the central clock mechanism (that so well accounts for normal functioning) is not destroyed, but rather disrupted. The disruption does not appear to be simple. Festination is a complex disturbance. There is a delayed initiation; a slow, laborious beginning to a sequence of movements; and, there is a gradual acceleration of the sequence. The results of the present investigation have shown this acceleration to be linear. The type of behaviour described here is highly suggestive of the performance by a 'stable' system which is sluggish in responding. In order to actually respond, the system needs to be adjusted: its threshold-to-respond needs to be lowered to a critical 'trigger' level. This could be achieved through positive feedback. Once the system is in operation, however, a progressive acceleration of each successive segment of the sequence is observed. This is suggestive of *continued*

positive feedback activity. Clearly further investigations of the role that the VL nucleus and of (for our present purposes) its most important connection with the pallidum, is required. McLennan (1971) has suggested that the chemistry of the ventrolateral nucleus is complex, but not critically dependent on dopamine. The nucleus receives fibres not only from the pallidum but from the cerebellum as well. Although the chemistry of the fibres is not yet known, it is known that these fibres have an excitatory effect on the nucleus. As pointed out in Chapter 2, ACh and noradrenaline both act as neurotransmitters in circuits from the ventrolateral nucleus to the (mesencephalic) reticular formation. Interestingly, ACh is implicated in the excitatory circuits, and noradrenaline, which is related to dopamine, in the inhibitory circuits.

To summarize: normally behaviour is regulated centrally and all behaviour is monitored and co-ordinated in synchrony with a central clock. In Parkinsonism the clock is disrupted. It is suggested that the VL nucleus of the thalamus and the pallidum and the striatum are all fundamentally implicated in the disruption. In order for the damaged system to function at all, of necessity it needs to re-establish an adequate control mechanism. It is argued that an asynchronous control model could most readily account for the type of control function that is

established in a system damaged by Parkinsonian-producing lesions. This type of model would account for the phenomena observed both before and after treatment.

Dopamine is a transmitter substance. No claims can sensibly be made that L-dopa treatment is able to totally ameliorate the disturbances of Parkinsonism. To redefine Parkinsonism as a dopamine deficiency syndrome is to partially explain the pathology. The degree to which L-dopa is able to benefit performance is clearly shown in this investigation. L-dopa helps the damaged system perform more efficiently without engendering any functional reorganization approximating to normal function. Irrespective of whether dopamine is replaced or not, the fundamental disruption (as manifest in festination) remains unaltered.

# BIBLIOGRAPHY


ADAM,H.M. (1969): The topology of brain amines - a review. In HOOPER,G. (Ed .): *Metabolism of Amines in the Brain.* London: Macmillan.

AFIFI,A., and W.W.KAELBER (1965): Efferent connections of the substantia nigra in the cat. *Expl. Neurol. 11:* 474.

ALBE-FESSARD,D., S.RAIEVA, and W.SANTIAGO (1967): Sur les relations entre substance noire et noyau caude . *J. Physiol. (Paris) 59:* 324.

ALLAN,C.M., J.W.TURNER, and M.GADEA-CIRIA (1966): Investigations into speech disturbances following stereotactic surgery for Parkinsonism. *Brit. J. of Disorders of Communication 1:* 55.

ALLISON,R.S. (1966): Perseveration as a sign of diffuse and focal brain damage. II. *Brit. med. J. 2:*1095.

ALLISON,R.S., and D.J.HURWITZ (1967): On perseveration in aphasics. *Brain 90:* 429.

AMIN,A.H., T.B.B.CRAWFORD, and J.H.GADDUM (1954): The distribution of substance P and 5-hydroxytryptamine in the central nervous system of the dog. *J. Physiol. 126:* 596.

ANDÉN,N.-E., A.CARLSSON, A.DAHLSTRÖM, K.FUXE, N.-A.HILLARP, and K.LARSSON (1964): Demonstration and mapping out of nigro-neostriatal dopamine neurons. *Life Sciences 3:* 523.

ANDÉN,N.-E., H.CORRODI, and K.FUXE (1969): Turnover studies using synthesis inhibition. In HOOPER,G. (Ed .): *Metabolism of Amines in the Brain.* London: Macmillan.

ANDÉN,N.-E., A.DAHLSTRÖM, K.FUXE, and K.LARSSON (1965): Further evidence for the presence of nigro-neostriatal dopamine neurons in the rat. *Amer. J. Anat. 116:* 329.

ANDÉN,N.-E., K.FUXE, B.HAMBERGER, and T.HÖKFELT (1966): A quantitative study on the nigro-striatal dopamine neuron system in the rat. *Acta physiol. scand. 67:* 306.

Anon. (1970): *Parkinson's Disease and the Parkinsonian Syndrome*. London: Roche.

Anon. (1972): *Parkinson's Disease: A compendium*. London: Roche.

ARBIT,J., B.BOSHES, and R.BLONSKY (1970): Behaviour and mentation changes during therapy. In, BARBEAU.A., and F.H.McDOWELL. (Eds.): *L-dopa and Parkinsonism*. Philadelphia: F.A.Davis.

ASIMOV,I., et al. (1965): *Stedman's Medical Dictionary*. 21st ed. Baltimore: Williams and Wilkins.

AXELROD,J. (1959): Metabolism of epinephrine and other sympathomimetic amines. *Physiol. Rev. 39:* 751.

BAK,I.J. (1967): The ultrastructure of the substantia nigra and caudate nucleus of the mouse and the cellular localization of catecholamines. *Exp. Brain Res. 3:* 40.

BARBEAU,A. (1962): The pathogenesis of Parkinson's disease: a new hypothesis. *Canad. Med. Ass. J. 87:* 802.

BARBEAU,A. (1969): L-dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Canad. Med. Ass. J. 101:* 791.

BARBEAU,A. (1969b): Parkinson's disease as a systematic disorder. In GILLINGHAM,J.F., and I.M.L.DONALDSON, (Eds.): *Third Sumposium of Parkinson's Disease*. Edinburgh and London: E. & S.Livingstone.

BARBEAU,A. (1970): Functions of the striatum. A new proposal based on experience with L-dopa in extrapyramidal disorders. In DE AJURIAGUERRA, J., and G.GAUTHIER (Eds.): *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: George; Paris: Masson.

BARBEAU,A. (1972): Dopamine and mental function. In MALITZ,S. (Ed.): *L-Dopa and Behaviour*. New York: Raven Press.

BARBEAU,A., T.L.SOURKES, and G.F.MURPHY (1962): Les catecholamines dans la maladie de Parkinson. In DE AJURIGUERRA,J. (Ed.): *Monoamines et Systeme Nerveux Centrale*. Geneva: George; Paris: Masson.

BAROLIN,G.S., H.BERNHEIMER, and O.HORNYKIEWICZ (1964): Seitenverschiedenes Verhalten des Dopamins (3-Hydroxytyramin) im Gehirn eines Falles von Hemiparkinsonismus. *Schweiz. Arch. Neurol. Psychiat. 94:* 241.

BEARDSLEY,J.W., and F.PULETTI (1971): Personality (MMPI) and Cognitive (WAIS) changes after Levodopa treatment: Occurrence in patients with Parkinson's disease. *Archives of Neurology 25(2):* 145.

BÉDARD,P., L.LAROCHELLE, A.PARENT. and L.J.POIRIER (1969): The nigro-striatal pathway: a correlative study based on neuroanatomical and neurochemical criteria in the cat and the monkey. *Exp. Neurol. 25:* 365.

BELL,D.S. (1968): Speech functions of the thalamus inferred from the effects of thalamotomy. *Brain 91:* 619.

BERNHEIMER,H. (1964): Distribution of homovanillic acid in the human brain. *Nature 204:* 587.

BERNHEIMER,H., W.BIRKMAYER, and O.HORNYKIEWICZ (1963): Zur Biochemie des Parkinson-Syndroms des Menschen. *Klin. Wschr. 41:* 465.

BERNHEIMER,H., W.BIRKMAYER, O.HORNYKIEWICZ, K.JELLINGER, and F.SEITELBERGER (1965): Zur Differenzeirung des Parkinson-Syndroms: Biochemisch-neurohistologische Vergleichsuntersuchungen. *Proc. 8th Internat. Congress of Neurology, Vienna 4:* 145.

BERNHEIMER,H., W.BIRKMAYER, O.HORNYKIEWICZ, K.JELLINGER, and F.SEITLEBERGER: Unpublished observations, cited in HORNYKIEWICZ (1971).

BERNHEIMER,H., and O.HORNYKIEWICZ (1965): Herabgesetzte Konzentration der Homovanillinsäure im Gehirn von parkinsonkranken Menschen als Ausdruck der Störung des zentralen Dopaminstoffwechsels. *Klin. Wschr. 43:* 711.

BERTLER,Å., and E.ROSENGREN (1959): Occurrence and distribution of dopamine in brain and other tissues. *Experimentia 15:* 10.

BERTLER,Å., and E.ROSENGREN (1959a): Occurrence and distribution of catecholamines in brain. *Acta physiol. scand. 47:* 350.

BIRKMAYER,W., and O.HORNYKIEWICZ (1961): Der L-3, 4-Dioxyphenylalanin (=DOPA) - Effekt bei der Parkinson-Akinese. *Wiener Klinische Wochenschrift 73:* 787.

BLASCHKO,H. (1959): The specific action of L-dopa decarboxylase. *J. Physiol. 96:* 50.

BLOOM,F.E., E.COSTA, and G.C.SALMOIRAGHI (1965): Anesthesia and the responsiveness of individual neurons of the caudate nucleus of the cat to acetlycholine, norepinephrine and dopamine administered by microelectrophoresis. *J. Pharmacol. 150:* 244.

BOGDANSKI,D.F., H.WEISSBACH, and S.UDENFRIEND (1957): The distribution of serotonin, 5-hydroxytryptophan decarboxylase, and monoamine oxidase in brain. *J. Neurochem. I:* 272.

BONDUELLE,M., and A.GUILLARD (1962): Traitement chirurgical de la maladie de Parkinson et des tremblements non-parkinsoniens. *Therapie 17:* 39.

BOWSHER,D. (1962): *Introduction to Neuroanatomy.* (Second Revised Printing.) Oxford: Blackwell Scientific Publications.

BRAIN,Lord W.RUSSELL (1964): *Clinical Neurology.* 2nd ed. London: Oxford Univ. Press.

BRAVO,G.J., C.PARERA, and G.SEIQUER (1966): *J. Neurosurg. 24:* 640.

BRODAL,A. (1969): *Neurological Anatomy in Relation to Clinical Medicine.* 2nd ed. New York, London and Toronto: Oxford University Press.

CALNE,D.B. (1970): *Parkinsonism: physiology, pharmacology and treatment.* London: Edward Arnold.

CANTER,G.J. (1961): *An investigation of the speech characteristics of a group of patients with Parkinson's disease*. Ph.D. thesis: Northwestern U.

CANTER,G.J. (1963): Speech characteristics of patients with Parkinson's disease. I. Intensity, pitch and duration. *J. Speech Hearing Dis. 28:* 221.

CANTER,G.J. (1965a): Speech characteristics of patients with Parkinson's disease. II. Physiologicial support for speech. *J. Speech Hearing Dis. 30:* 44.

CANTER,G.J. (1965b): Speech characteristics of patients with Parkinson's disease. III. Articulation, diadochokinesis, and overall speech adequacy. *J. Speech Hearing Dis. 30:* 217.

CARLSSON,A. (1959): The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol. Rev. 11:* 490.

CARLSSON,A. (1971): Basic concepts underlying recent developments in the field of Parkinson's disease. In McDOWELL,F.H., and C.H.MARKHAM (Eds.): *Recent Advances in Parkinson's Disease*. Oxford: Blackwell Scientific Publications.

CARLSSON,A., B.FALCK, and N.-Å.HILLARP (1962): Cellular localization of brain monoamines. *Acta physiol. scand. 56:* suppl. 196: 1.

CARLSSON,A., and M.LINDQVIST (1962): *In-vivo* decarboxylation of α-methyl dopa and α-methyl-metatyrosine. *Acta physiol. scand. 54:* 87.

CARLSSON,A., M.LINDQVIST, and T.MAGNUSSON (1957): 3, 4-Dihydroxyphenylalanine and 5-hydroxytrytophan as reserpine antagonists. *Nature 180:* 1200.

CARLSSON,A., M.LINDQVIST, T.MAGNUSSON, and B.WALDECK (1958): On the presence of 3-hydroxytyramine in brain. *Science 127:* 471.

CARLSSON,A., and B.WALDECK (1964): A method for the fluorimetric determination of 3-methoxytramine in tissues on the occurrence of this amine in brain. *Scand. J. clin. Lab. Inv. 16:* 113.

CARMAN,J.B., W.M.COWAN, and T.P.S.POWELL (1963): The organization of the cortico-striate connexions in the rabbit. *Brain 86:* 525.

CARMAN,J.B., W.M.COWAN, T.P.S.POWELL, and K.E.WEBSTER (1965): A bilateral cortico-striate projection. *J. Neurol. Neurosurg. Psychiat. 28:* 71.

CARPENTER,M.B., and R.E.McMASTERS (1964): Lesions of the substantia nigra in the Rhesus monkey. Efferent fiber degeneration and behavioural observation. *Amer. J. Anat. 114:* 293.

CARPENTER,M.B., and N.L.STROMINGER (1967): Efferent fibers of the subthalamic nucleus in the monkey. A comparison of the efferent projections of the subthalamic nucleus, substantia nigra and globus pallidus. *Amer. J. Anat. 121:* 41.

CHARCOT,R. (1887): *Leçons du Mardi à la Salpetrière*. Paris: V.A.Delahaye et Cie.

COLE,M.F., and M.COLE (Eds. & translators) (1971): *Pierre Marie's Papers on Speech Disorders*. New York: Hafner.

COLE,M., W.J.H. NAUTA, and W.H.MEHLER (1964): The ascending efferent projections of the substantia nigra. *Trans. Amer. Neurol. Ass. 89:* 74.

CONNOR,J.D. (1968): Caudate unit responses to nigral stimuli: evidence for a possible nigro-neostriatal pathway. *Science 160:* 899.

COOKE,J. (1820-1823): *Treatise on Nervous Disease*. London: for Longman, Hurst, Rees, Orme and Brown.

COOPER,I.S. (1954): Surgical occlusion of the anterior choroidal artery in parkinsonism. *Surg. Gynec. Obstet. 99:* 207.

COOPER,I.S. (1956a): Clinical results and follow-up studies in a personal series of 300 operations for Parkinsonism. *J. Amer. Geriat. Soc. 4:* 1171.

COOPER,I.S. (1956b): *The Neurosurgical Alleviation of Parkinsonism.* Springfield: Charles C.Thomas.

COOPER,I.S. (1960): Results of 1000 consecutive basal ganglia operations for parkinsonism. *Arch. Intern. Med. (Chicago) 52:* 483.

COOPER,I.S. (1961): *Parkinsonism: Its Medical and Surgical Therapy.* Springfield: Charles C.Thomas.

COTZIAS,G.C., P.S.PAPAVASILIOU, and R.GELLENE (1969a): Modification of parkinsonism: Chronic treatment with L-Dopa. *New Engl. J. of Medicine 280(7):* 337.

COTZIAS,G.C., P.S.PAPAVASILIOU, R.GELLENE, R.B.ARONSON, and I.MENA (1969): Long term effects of Dopa on Parkinsonism: A proposal. In GILLINGHAM,F.J., and I.M.L.DONALDSON (Eds.): *Third Symposium on Parkinson's Disease.* Edinburgh and London: E. & S.Livingstone.

COTZIAS,G.C., M.H.VAN WOERT, L.M.SCHIFFER (1967): Aromatic amino acids and modification of parkinsonism, *New Engl. J. Med. 276:* 374.

COWAN,W.M., and T.P.S.POWELL (1966): Striopallidal projection in the monkey. *J. Neurol. Neurosurg. Psychiat. 29:* 426.

CRAMER,W. (1940): De spraak bij Patienten met Parkinsonisme. *Logopaedie en Phoniatrie 22:* 17.

CRITCHLEY,M. (1929): Arteriosclerotic Parkinsonism. *Brain 52:* 23.

CRITCHLEY,M. (1955): Introduction. In CRITCHLEY,M. (Ed.): *James Parkinson (1755-1824): a bicentenary volume of papers dealing with Parkinson's disease, incorporating the original 'Essay on the Shaking Palsy'.* London: Macmillan.

CRUCHET,R., MOUTIER, and CALMETTE (1917): Forty cases of subacute encephalomyelitis. *Bull. et Mém. Soc. méd. Hôp. de Paris 41:* Cited in Hall (1924).

DAHLSTRÖM,A., and K.FUXE (1964): Evidence for the existence of monoamine-containing neurones in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurones. *Acta physiol. scand. 62:* suppl. 232: 1.

DARLEY,F.L., A.E.ARONSON, and J.R.BROWN (1969a): Differential diagnostic patterns of dysarthria. *J. Speech Hearing Res. 12:* 246.

DARLEY,F.L., A.E.ARONSON, and J.R.BROWN (1969b): Clusters of deviant speech dimensions in the dysarthrias. *J. Speech Hearing Res. 12:* 462.

DAVIS,R. (1966): Acetylcholine-sensitive neurones in ventrolateral thalamic nucleus. In PURPURA,D.P. and M.D.YAHR (Eds.): *The Thalamus*. New York: Columbia University Press.

DE AJURIAGUERRA,J. (1971): La notion d'akinésie. In DE AJURIAGUERRA,J., and G.GAUTHIER (Eds.): *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Geneva: George; Paris: Masson.

DEGWITZ,R., R.FROWEIN, C.KULENKAMPFF, and U.MOHS (1960): Über die Wirkungen des L-DOPA beim Menschen und deren Beeinflussung durch Reserpin, Chlorpromazin, Ipromazid und Vitamin $B_6$. *Klin. Wschr. 38:* 120.

DEJERINE, (1908): Contributions to: Discussion of Aphasia. Society of Neurology of Paris. Meeting of June 11, 1908. *Revue Neurol. 16:* 1. In COLE and COLE (Eds. & tanslators), 1971.

DEJONG,R.N. (1967): *The Neurological Examination*. 3rd ed. New York: Harper & Row.

DE LA TORRE,R., M.MIER, and B.BOSHES (1960): Studies in Parkinsonism: evaluation of respiratory function - preliminary observations. *Quart. Bull. (Northwestern Univ. Med. School) 34:* 232.

DENNY-BROWN,D.E. (1960a): Diseases of the basal ganglia: their relation to disorders of movement. *Lancet:* 1099.

DENNY-BROWN,D.E. (1960b): Diseases of the Basal Ganglia: their relation to disorders of movement. From the Croonian lectures for 1960. *Lancet:* 1155.

DENNY-BROWN,D.E. (1962): *The Basal Ganglia and Their Relation to Disorders of Movement.* Oxford: Univ. Press.

DENNY-BROWN,D.E. (1968): In: VINKEN,P.J. and G.W.BRUYN (Eds.): *Diseases of the Basal Ganglia.* Amsterdam: North Holland Publishing Co.

DENNY-BROWN,D.E. (1969): The rigidity of Parkinsonism. In GILLINGHAM,J.F., and I.M.L.DONALDSON (Eds.): *Third Symposium on Parkinson's Disease.* Edinburgh and London: E. & S.Livingstone.

DESIRAJU,T., and D.P.PURPURA (1969): Synaptic convergence of cerebellar and lenticular projections to thalamus. *Brain Res. 15:* 544.

DE VITO,J.L., and O.A.SMITH, Jr. (1964): Subcortical projections of the prefrontal lobe of the monkey. *J. comp. Neurol. 123:* 413.

DILLAR,L., and M.RIKLAN (1956): Psychosocial factors in Parkinson's disease. *J. Amer. Geriat. Soc. 4:* 1291.

DONNELLY,E.F., and T.N.CHASE (1973): Intellectual and memory function in parkinsonian and non-parkinsonian patients treated with L-dopa. *Diseases of the Nervous System 34(2):* 119.

DUVIOSIN,R.C. (1967): Cholinergic-anticholinergic antagonism in parkinsonism. *Arch. Neurol. 17:* 124.

ECCLES,J. (1964): *The Physiology of Synapses.* Berlin: Springer.

EHRINGER,H., and O.HORNYKIEWICZ (1960): Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Klin. Wschr. 38:* 1236.

FAGER,C.A. (1968): Evaluation of thalamic and subthalamic surgical lesions in the alleviation of Parkinson's disease. *J. Neurosurg. 28:* 145.

FAHN,S., and L.J.CÔTÉ (1968): Regional distribution of choline acetylase in the brain of the rhesus monkey. *Brain Res. 7:* 323.

FELDBERG,W., and M.VOGT (1948): Acetylcholine synthesis in different regions of the central nervous system. *J. Physiol. 107:* 372.

FELTZ,P. (1969): Dopamine, amino acids and caudate unitary responses to nigral stimulation. *J. Physiol. 205:* 8.

FERRARD,A. (1925): Contributo sperimentale allo studio della substantia nigra normale e dei suoi rapporti con la corteccia cerebale e con il corpo striato. *Arch. gen. Neurol. Psychiat. (Lond.) 6:* 26.

FERRARO,A. (1928): The connections of the pars suboculomotoria of the substantia nigra. *Arch. gen. Neurol. Psychiat. (London) 19:* 117.

FOIX,C., and J.NICOLESCO (1925): *Anatomie cérébrale. Les noyaux gris centraux et la region mésencéphalo - sous optique.* Paris: Masson.

FRIGYESI,T.L., and D.P.PURPURA (1967): Electrophysiological analysis of reciprocal caudato-nigral relations. *Brain Res. 6:* 440.

FUENFGELD,E.W. (1961): Die psychischen Hirnfunktionen bei Hirnatrophischen Zustandsbildern nach operativer Belastung (stereotaktische Hirnoperationen aelter Parkinsonpatienten). *Acta Neurochir. (Wien) 7:* 539.

FUXE,K. (1965): Evidence for the existence of monoamine neurones in the central nervous system. IV. Distribution of monoamine nerve terminals in the central nervous system. *Acta physiol. scand. 64:* suppl. 247: 39.

FUXE,K (1965a): Evidence for the existence of monoamine neurones in the central nervous system. III. The monoamine nerve terminals. *Z. Zellforsch. 65:* 573. Cited in Fuxe et al. (1969).

FUXE,K., B.HAMBERGER, and T.HÖKFELT (1968): Distribution of noradrenaline nerve terminals in cortical areas of the rat. *Brain Res. 8:* 125.

FUXE,K., T.HÖKFELT, and U.UNGERSTEDT (1969): Distribution of monoamines in the mammalian central nervous system by histochemical studies. In HOOPER,G. (Ed.): *Metabolism of Amines in the Brain.* London: Macmillan.

GILLINGHAM,F.J. (1960-1961): Surgical treatment of parkinsonism. *Trans. Med. Soc. London 77:* 52.

GILLINGHAM,F.J. (1969): Introduction to the scientific session. In GILLINGHAM,F.J., and I.M.L.DONALDSON (Eds.): *Third Symposium on Parkinson's Disease.* Edinburgh and London: E. & S.Livingstone.

GILLINGHAM,F.J., S.KALYANARAMAN, and A.A.DONALDSON (1964): Bilateral stereotaxic lesions in the management of parkinsonism and the dyskinesias. *Br. med. J. 2:* 656.

GILLINGHAM,J.F., W.S.WATSON, A.A.DONALDSON, and J.A.L. NAUGHTON (1960): The surgical treatment of parkinsonism. *Br. med. J. 2:* 1395.

GLEES,P. (1944): The anatomical basis of cortico-striate connections. *J. Anat. (Lond.) 78:* 47.

GLOWINSKI,J., L.L.IVERSEN, and J.AXELROD (1965): Regional distribution and metabolism of $H^3$-norepinephrine (NE) and $H^3$dopamine (DM) in the rat brain. *The Pharmacologist 7:* No. 2.

GOLDFLAM,S. (1920): Przyczynek do rozorodnosci postaei zapalenia mozgu pochodzenia neiropnego. *Lekarz Wojsk. 1:* 1. Cited in Hall (1924).

GOLDMAN EISELR,F. (1968): *Psycholinguistics.* London and New York: Academic Press.

GOLDSTEIN,K. (1948): *Language and Language Disturbance.* New York: Grune and Stratton.

GOWERS,W.R. (1886-1888): *A Manual of Diseases of the Nervous System.* London: J. and A.Churchill.

GOWERS,W.R. (1910): *A System of Medicine*. Vol. 8. 2nd ed. London: Macmillan. Cited by Walshe (1955).

GREENFIELD,J.G. (1955): The pathology of Parkinson's disease. In CRITCHLEY, M. (Ed.): *James Parkinson (1755-1824). A bicentenary volume of papers dealing with Parkinson's Disease, incorporating the original 'Essay on the Shaking Palsy'*. London: Macmillan.

GREENFIELD,J.G., and F.D.BOSANQUET (1953): The brain-stem lesions in Parkinsonism. *J. Neurol. Neurosurg. Psychiat. 16:* 213.

GREWEL,F. (1956): Classification of dysarthrias. *Acta psychiat. neurol. Scand. 32.*

GREWEL,F. (1957): Dysarthria in post-encephalitic parkinsonism. *Acta psychiat. neurol Scand. 4:* 440.

GREY,E.C. (1967): The Synapse. *Science J. 3:* 66.

GUIOT,G., F.HERTZOG, P.RONDOT, and P.MOLINA (1961): Arrest or acceleration of speech by thalamic stimulation in the course of stereotacix procedures for parkinsonism. *Brain 84:* 363.

HALL,A.J. (1924): *Epidemic Encephalitis (Encephalitis Lethargica)*. Bristol: John Wright & Sons.

HANKINSON,J. (1969): Stereotactic surgery. In, the late Lord BRAIN and M.Wilkinson (Eds.): *Recent Advances in Neurology and Neuropsychiatry*. 8th ed. London: J. & A. Churchill.

HASSLER,R. (1938): Zur Pathologie der Paralysis Agitans und des postencephalitischen Parkinsonismus. *J. Psychol. Neurol. (Leipzig) 48:* 387.

HASSLER,R. (1949): Uber die afferenten Bahnen und Thalamuskerne des motorischen Systems des Grosshirns. *Arch. Psychiat. Nervenkr. 182:* 759-785; 786-818. Cited by Brodal,A. (1969).

HASSLER,R. (1953): Extrapyramidal-motorische Syndrome und Erkrankungen. In BERGMANN,G.V., W.FREY, H.SCHWIEGK, and R.JUNG (Eds.): *Handbuch der inneren Medizin Vol V.* Berlin: Springer.

HASSLER,R. (1966): Thalamic regulation of muscle tone and the speed of movements. In PURPURA,D.P., and M.D.YAHR (Eds.): *The Thalamus*. New York: Columbia Univ. Press.

HASSLER,R., and I.J.BAK (1969): Unbalanced ratios of striatal dopamine and serotonin after experimental interruption of strionigral connections in rat. In GILLINGHAM,F.J., and I.M.DONALDSON (Eds.): *Third Symposium on Parkinson's Disease*. Edinburgh and London: E. & S.Livingstone.

HEAD,H. (1926): *Aphasia and Kindred Disorders of Speech. Vol. 1*. Cambridge Univ. Press.

HEBB,C.O., G.M.LING, E.G.McGEER, P.L.McGEER, and D.PERKINS (1964): Effect of locally applied hemicholinium on the acetylcholine content of the caudate nucleus. *Nature 204:* 1309.

HERMANN,K. J.W.TURNER, F.J.GILLINGHAM, and R.M.GAZE (1966): The effects of destructive lesions and stimulation of the basal ganglia on speech mechanisms. *Confin. neurol. 27:* 197.

HERZ,A., and W.ZIEGLGÄNSBERGER (1968): The influence of microelectrophoretically applied biogenic amines, cholinomimetics and procaine on synaptic excitation in the corpus striatum. *Int. J. Neuropharmacol. 7:* 221.

HOKFELT,T. (1968): *In vitro* studies on central and peripheral monoamine neurons at the ultrastructural level. *Z. Zellforsch. mikrosk. Anat. 91:* 1.

HOLTZ,P. (1959): Role of L-dopa decarboxylase in the biosynthesis of catecholamines in nervous tissue and the adrenal medulla. *Pharmacol. Rev. 11:* 317.

HOLTZ,P. and E.WESTERMANN (1956): Über die Dopadecarboxylase und Histidindecarboxylase des Nervengewebes. *Arch. exp. Path. Pharmak. 227:* 538. Cited in HORNYKIEWICZ (1966).

HOLZBAUER,M., and M.VOGT (1956): Depression by reserpine of the noradrenaline concentration in the hypothalamus of the cat. *J. Neurochem. 1:* 8.

HOLZER,G., and O.HORNYKIEWICZ (1959): Uber den Dopamin-(Hydroxytyramin-) Stoffwechsel im Gehim der Ratte. *Arch. exp. Path. Pharmak. 237:* 27. In HORNYKIEWICZ (1966).

HORNYKIEWICZ,O. (1963): Die topishe Lokalisation und das Verhalten von Noradrenalin und Dopamin (3-Hydroxytyramin) in der Substantia nigra des normalen und Parkinsonkranken Menschen. *Wien. Klin. Wschr. 75:* 309. In HORNYKIEWICZ (1971).

HORNYKIEWICZ,O. (1964): The role of dopamine (3-hydroxytyramine) in parkinsonism. In TRABUCCHI,E., R.PAOLETTI, and N.CANAL (Eds.): *Biochemical and Neurophysiological Correlations of Centrally Acting Drugs.* New York: Pergamon Press.

HORNYKIEWICZ,O. (1966): Dopamine (3-hydroxytyramine) and brain function. *Pharmacol. Review 18:* 925.

HORNYKIEWICZ,O. (1970): How does L-dopa work in Parkinsonism? In BARBEAU,A., and F.H.McDOWELL (Eds.): *L-dopa and Parkinsonism.* Philadelphia: A.Davis.

HORNYKIEWICZ,O. (1971a): Histochemistry, biochemistry, and pharmacology of brain catecholamines in extrapyramidal syndromes in man. In DE AJURIAGUERRA,J., and G.GAUTHIER (Eds.): *Monoamines Noyaux Gris Centreaux et Syndrome de Parkinson.* Geneva: George; Paris: Masson.

HORNYKIEWICZ,O. (1971b): Neurochemical pathology and pharmacology of brain dopamine and acetylcholine: rational basis for the current drug treatment of Parkinsonism. In McDOWELL,F.H., and C.H.MARKHAM (Eds.): *Recent Advances in Parkinson's Disease.* Oxford: Blackwell Scientific Publications.

HORNYKIEWICZ,O., H.J.LISCH, and A.SPRINGER (1968): Homovanillic acid in different regions of the human brain: attempt at localizing central dopamine fibres. *Brain Res. 11:* 662.

JACKSON,J.H. (1866): Notes on the physiology and pathology of language. *Med. Times and Gazette 1:* 659. In TAYLOR,J. (Ed.) (1932): *Selected Writings of John Hughlings Jackson.* Vol. 2. London: Hodder & Stoughton.

JOHNSON,T.N., and C.D.CLEMENTE (1959): An experimental study of the fiber connections between the putamen, globus pallidus, ventral thalamus, and midbrain tegmentum in cat. *J. Comp. Neurol. 113:* 83.

JOHNSON,W., F.L.DARLEY, and D.C.SPRIESTERSBACH (1952): *Diagnostic Methods in Speech Pathology*. New York Evanston: Harper & Row.

JUNG,R., and R.HASSLER (1960): The extrapyramidal motor system. In FIELD.J., H.W.MAGOUN, and V.E.HALL (Eds.): *Handbook of Physiology. Sect. 1. Vol. 11*. Washington: American Physiological Society.

JURKO,M.F., and O.J.ANDY (1964): Psychological aspects of diencephalotomy. *J. Neurol. Neurosurg. and Psychiat. 27:* 516.

KENDALL,M.G. (1948): *Rank Correlation Methods*. London: Griffin.

KOHS,S.C. (1923): *Intelligence Measurement*. New York: Macmillan.

KRAYENBÜHL, J.SIEGRFIED, M.KOHENOF, and M.G.YASARGIL (1965): Is there a dominant thalamus? *Confin. neurol. 26:* 246.

KRAYENBUHL,H., and M.G.YASARGIL (1961): Ergebnisse der stereotaktischen Operationen beim Parkinsonismus, insbesondere der doppelseitigen Eingriffe. *Deutsch. Z. Nervenheilk. 182:* 530.

LAITINEN,L. (1966): Thalamic targets in stereotaxic treatment of Parkinson's disease. *J. Neurosurg. 24:* 82.

LASHLEY,K.S. (1951): The problem of serial order in behaviour. In JEFFRESS,L.A.(Ed.): *Cerebral Mechanisma in Behaviour*. The Hixon Symposium. New York: John Wiley and Sons.

LASZEWSKI,Z. (1956): Role of the Department of Rehabilitation in the pre-operative evaluation of Parkinsonian patients. *J. Amer. Geriat. Soc. 4:* 1280.

LAVERTY,R., and D.F.SHARMAN (1965): Modification by drugs of the metabolism of 3, 4-dihydroxyphenylthylamine, noradrenaline and 5-hydroxytryptamine in the brain. *Brit. J. Pharmacol. 24:* 759.

LENNEBERG,E.H. (1967): *Biological Foundations of Language.* New York, London and Sydney: John Wiley & Sons.

LEVITT,M., S.SPECTOR, A.SJOERDSMA, and S.UDENFRIEND (1965): Elucidation of the rate-limiting step in norepinephrine biosynthesis in the perfused guinea pig heart. *J. Pharmacol. 148:* 1.

LEYSER,E. (1924): Uber einige Formen von dysarthrischen Spannungen und die extra-pyramidale Pseudobulbarparalyse (Akinetisch-hypertonisches Bulbärsyndrom). *Zietsch. f. d.ges. Neur. u. Psych. 70:* 35.

LIN,T.H., and I.S.COOPER (1960): Results of chemo-pallidectomy and chemothalamectomy: a study of one hundred cases of parkinsonism, with ages over sixty. *AMA Arch. Neurol. 2:* 188.

LINDSLEY,D.B., L.H.SCHREINER, and H.W.MAGOUN (1949): An electromyographic study of spasticity. *J. Neurophysiol. 12:* 197.

LLAMAS,A., and F.REINOSO-SUÁREZ (1969): Projections of the substantia nigra and ventral tegmental mesencephalic area. In GILLINGHAM,F.J., and I.M.L.DONALDSON (Eds.): *Third Symposium on Parkinson's Disease.* Edinburgh and London: E. & S.Livingstone.

LLOYD,K., and O.HORNYKIEWICZ (1970): Parkinson's disease: activity of L-Dopa decarboxylase in discrete brain regions. *Science 170:* 1212.

LORANGER,A.W., et al. (1973): Parkinsonism, L-dopa, and intelligence. *Amer. J. of Psychiatry 130(12):* 1386.

McCANCE,I., J.W.PHILLIS, and R.A.WESTERMAN (1968): Acetylcholine-sensitivity of thalamic neurones: its relationship to synaptic transmission. *Brit. J. Pharmacol. 32:* 635.

McFIE,J. (1960): Psychological effects of stereotaxic operations for the relief of parkinsonian symptoms. *J. Ment. Sci. 106:* 1521.

McHENRY,L.C. (1969): *Garrison's History of Neurology.* Revised and enlarged ed. Springfield: Charles C.Thomas.

MacINTOSH,F.C. (1941): The distribution of acetylcholine in the peripheral and central nervous system. *J. Physiol. 99:* 436.

McLENNAN,H. (1963): *Synaptic Transmission.* 1st ed. Philadelphia: Saunders.

McLENNAN,H. (1964): The release of acetylcholine and of 3-hydroxytyramine from the caudate nucleus. *J. Physiol. 174:* 152.

McLENNAN,H. (1965): The release of dopamine from the putamen. *Experimentia 21:* 725.

McLENNAN,H. (1971): Possible chemical mediators of synaptic action in certain basal ganglia pathways. In McDOWELL,F.H., and C.H.MARKHAM (Eds.): *Recent Advances in Parkinson's Disease.* Oxford: Blackwell Scientific Publications.

McLENNAN,H., R.D.HUFFMAN, and K.C.MARSHALL (1968): Patterns of excitation of thalamic neurones by amino-acids and by acetylcholine. *Nature 219:* 387.

McLENNAN,H. and D.H.YORK (1966): Cholinergic mechanisms in the caudate nucleus. *J. Physiol. 187:* 163.

McLENNAN,H., and D.H.YORK (1967): The action of dopamine on neurones of the caudate nucleus. *J. Physiol. 189:* 393.

MAGOUN,H.W., and R.RHINES (1946): An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol. 9:* 165.

MALLIANI,A., and D.P.PURPURA (1967): Intracellular studies of the corpus striatum. II. Patterns of synaptic activities in lenticular and entopenduncular neurons. *Brain Res. 6:* 341.

MARIE,P. (1906a): The third left frontal convolution plays no special role in the function of language. *Semaine Medicale 26:* 241. In COLE & COLE (Eds. & translators), 1971.

MARIE,P (1906b): What to think about subcortical aphasias (pure aphasias). *Semaine Medicale 26:* 493. In COLE & COLE (Eds. & translators), 1971.

MARIE,P. (1906c): Aphasia from 1861 to 1866. Essay of historical criticism on the genesis of the doctrine of aphasis. *Semaine Medicale 26:* 565. In COLE & COLE (Eds. & translators), 1971.

MARIE,P. (1906d): A case of transitory anarthria by lesion of the lenticular zone. *Bulletins et Memories de la Societe Medicale des Hopitaux de Paris, Ser. 3, 23:* 1291. In COLE & COLE (Eds. & translators), 1971.

MARIE,P. (1907): On the function of language. Corrections concerning the article of Grasset. *Revue de Philosophie 10:* 207. In COLE and COLE (Eds. & translators), 1971.

MARIE ,P. (1908 a): Contribution to: Discussion on aphasia. Society of Neurology of Paris. Meeting of June 11, 1908. *Revue Neurologique 16:* 1. In COLE and COLE (Eds. & translators), 1971.

MARIE,P. (1908b): Contribution to Third discussion on aphasia. Society of Neurology of Paris. Meeting of July 23, 1908. *Rev. neurol. 16:* 1025. In COLE and COLE (Eds. & translators), 1971.

MARIE,P. (1917): The aphasias of war. *Rev. neurol. 31/32:* 53. In COLE and COLE (Eds. & translators), 1971.

MARIE,P., and G.LEVY (1925): A singular trouble with speech: palilalia (dissociation of voluntary speech and automatic speech). *Le Monde Medicale 664:* 329. In COLE and COLE (Eds. & translators), 1971.

MARKHAM,C.H., and R.W.RAND (1963): Stereotactic surgery in Parkinson's disease. *Arch. neurol. (Chicago) 8:* 621.

MARSH,G.G., C.M.MARKHAM, and R.ANSEL (1971): Levodopa's awakening effect on patients with parkinsonism. *J. of Neurol., Neurosurg. and Psychiat. 34(3):* 209.

MARTIN,J.P. (1959): Remarks on the functions of the basal ganglia. *Lancet 1:* 999.

MASSION,J. (1967): The mammalian red nucleus. *Physiol. Rev. 47:* 383.

MASUOKA,D.T., H.F.SCHOTT, and L.PETRIELLO (1963): Formation of catecholamines by various areas of cat brain. *J. Pharmacol. 139:* 73.

MATHEWS,W.B., P.M.BECK, W.B.DANIEL, D.L.STEVENS, M.M.PALPERS, D.M.ASHER, D.C.GAJDUSEK, and C.J.GIBBS Neuropathology of a transmission experiment. *Brain 92:* 699.

MAWDSLEY,C. (1970): The medical treatment of Parkinsonism. *Clinica Europea:* 111.

MAWDSLEY,C., and C.V.GAMSU (1971): Periodicity of speech in Parkinsonism. *Nature 231:* 315.

MAWDSLEY,C., I.R.WILLIAMS, I.A.PULLAR, D.L.DAVIDSON, and N.E.KINLOCH (1972): Treatment of Parkinsonism by amantadine and levodopa. *Clin. pharmacol, and therapeutics 13:* 575.

MEGNA,G.F., et al. (1971): The Rey's test in the evaluation of some L-dopa induced effects in parkinsonians. *Acta Neurol. 26(4):* 473.

MERRITT,H.H., (1954): Parkinsonism and its treatment. In DOSHAY,L.J. (Ed.): *Parkinsonism and Its Treatment* Philadelphia: Lippincott.

METTLER,F.A. (1945): Fiber connections of the corpus striatum of the monkey and baboon. *J. Comp. Neurol. 82:* 169.

METTLER,F.A. (1964): Substantia nigra and Parkinsonism. *Arch. Neurol. (Chic.) 11:* 529.

METTLER,F.A. (1967): In, YAHR, M.D., and D. P. PURPURA (Eds.): *Neurophysiological Basis of Normal and Abnormal Motor Activities*. New York: Raven Press.

MEYER,M. (1949): A study of efferent connexions of the frontal lobe in the human brain after leucotomy. *Brain 72:* 265.

MEYERS,R. (1953): The extrapyramidal system. An inquiry into the validity of the concept. *Neurology (Minneap.) 3:* 627.

MOLINA,P. (1965): *Connexiones nigro-corticales*. Thesis Doctoral. University of Navarra. Cited by Llamas and Reinoso-Suárez (1969).

MONAKOW,C. von (1822): Über einige durch Exstirpation circumscripter Hirnrindenregion bedingte Entwicklungshemmungen des Katinchengehirns. *Arch. Psychiat. Nervkrankh. 12:* 141. Cited by Llamas and Reinoso-Suárez (1969).

MONAKOW,C. von (1895): Experimentelle und pathologischanatomische Untersuchungen über die Haubenregion, den Sehhugel und die Regio subthalamica. *Arch. Psychiat. Nervkrankh. 27:* 1.

MOUNTCASTLE,V.B. (1962): *Interhemispheric Relations and Cerebral Dominance*. Baltimore: Johns Hopkins Press.

MUELLER,C., and M.G.YASARGIL (1959): Zur psychiatrie der stereotaktischen Hirnoperationen bei extra-pyramidalen Erkrankungen. *Schweiz. Arch. Neurol. Psychiat. 84:* 136.

MUNDINGER,F., and T.RIECHERT (1963): Die stereotaktischen Hirnoperationen zur Behandlung extrapyramidaler Bewegungsstörungen (Parkinsonismus und Hyperkinesen) und ihre Resultate. *Fortschr. Neurol. Psychiat. 31:* 1.

NAKANO,K.K., H.ZUBICK, and R.H.TYLER (1973): Speech defects of parkinsonian patients: Effects of levodopa therapy on speech intelligibility. *Neurology 23(8):* 865.

NAUTA,W.J.H., and W. R.MEHLER (1966): Projection of the lentiform nucleus in the monkey. *Brain Res. 1:* 3.

NAUTA,S.J.H., and D.G.WHITLOCK (1954): An anatomical analysis of the non-specific thalamic projection system. In DELAFRESNAYE,J.F. (Ed.): *Brain Mechanisms and Consciousness*. Oxford: Blackwell.

NEWCOMBE,F., R.C.OLDFIELD, G.G.RATCLIFF, and A.WINGFIELD (1971): Recognition and naming of object-drawings by men with focal brain wounds. *J. Neurol. Neurosurg. Psychiat. 34:* 329.

NEWCOMBE,F., R.C.OLDFIELD, and A.WINGFIELD (1965): Object-naming by dysphasic patients. *Nature 207:* 1217.

NOYES,A.P. (1953): *Modern Clinical Psychiatry*. 4th ed. Philadelphia: W.B.Saunders.

NUGENT,C.A., et al. (1958): Dyspnea as a symptom in Parkinson's disease. *Amer. Rev. Tuberculosis 78:* 682.

OJEMAN,G.A., K.I.BLICK, and A.A.WARD (1971): Improvement and disturbance of short-term verbal memory with human ventrolateral thalamic stimulation. *Brain 94:* 225.

OJEMAN,G.A., and P.FEDIO (1968): Effect of stimulation of the human thalamus and parietal and temporal white matter on short-term memory. *J. Neurosurg. 29:* 51.

OJEMAN,G.A., P.FEDIO, and J.M.VAN BUREN (1968): Anomia from pulvinar and subcortical parietal stimulation. *Brain 91:* 99.

OJEMAN,G.A., and A.A.WARD (1971): Speech representation in ventrolateral thalamus. *Brain 94:* 669.

OLDFIELD,R.C., and A.WINGFIELD (1964): The time it takes to name an object. *Nature* 202: 1031.

OLDFIELD,R.C., and A.WINGFIELD (1965): A series of pictures for use in object-naming. M.R.C. Psycholinguistics Research Unit. Special Report No. PLU/65/19.

OLIVIER,A., A.PARENT, H.SIMARD, and L.J.POIRIER (1970): Cholinesterase striatopallidal and striatonigral efferents in the cat and the monkey. *Brain Res. 18:* 273.

ORDENSTEIN,L. (1867): *Sur la paralysie agitante et la sclérose en plaques généralisee*. M.D.thése. Paris: Martinet.

PARENT,A., and L.J.POIRIER (1969): The medial forebrain bundle (MFB) and ascending monoaminergic pathways in the cat. *Canad. J. Physiol. Pharmacol. 47:* 781.

PARIGI,S., F.ANGELERI, and F.FERRO-MILONE (1964): Effetti sensoriali uditivi e verbomotori coatti da stimolazione dei nuclei talamici di relais extrapiramidale. *Rivista di Neurobiologia 10:* 81.

PARKINSON,J. (1817): *An Essay on the Shaking Palsy*. London: Sherwood, Neeley and Jones.

PEACHER,W.G. (1950): The etiology and differential diagnosis of dysarthria. *J. Speech Hearing Dis. 15:* 252.

PENFIELD,W. (1936): The cerebral cortex and consciousness. The Harvey Lecture. Reprinted in *Arch. Neurol. Psychiat. (Chicago) 40:* 417-442, 1938.

PENFIELD,W. (1952): Epileptic automatism and the centrencephalic system. *Rev. Publ. Assoc. Nerv. ment. Dis. 30:* 513.

PENFIELD,W., and L.ROBERTS (1959): *Speech and Brain-Mechanisms*. Princeton: Princeton Univ. Press.

PHILLIS,J.W., and A.K.TEBÉCIS (1967): The responses of thalamic neurones in iontophoretically applied monoamines. *J. Physiol. 192:* 715.

POIRIER,L.J. (1971): The development of animal models for studies in Parkinson's disease. In McDOWELL,F.H., and C.H.MARKHAM (Eds.): *Recent Advances in Parkinson's Disease*. Oxford: Blackwell Scientific Publications.

POIRIER,L.J., P.BÉDARD, R.BOUCHER, G.BOUVIER, L.LAROCHELLE, A.OLIVIER, and P.SINGH (1969a): The origin of different striato- and thalamopetal neuro-chemical pathways and their relationship to motor activity. In GILLINGHAM,F.J., and I.M.L.DONALDSON (Eds.): *Third Symposium on Parkinson's Disease*. Edinburgh and London: E. & S.Livingstone.

POIRIER,L.J., and G.BOUVIER (1966): The red nucleus and its efferent nervous pathways in the monkey. *J. comp. Neurol. 128:* 223.

POIRIER,L.J., G.BOUVIER, P.BÉDARD, R.BOUCHER, L.LAROCHELLE, A.OLIVIER, and P.SINGH (1969b): Essai sur les circuits neuronaux impliqués dans le tremblement postural et l'hypokinesie. *Rev. Neurol. 120:* 15.

POIRIER,L.J., and T.L.SOURKES (1965): Influence of the substantia nigra on the catecholamine content of the striatum. *Brain 88:* 181.

POWELL,T.P.S., and W.M.COWAN (1956): A study of thalamo-striate relations in the monkey. *Brain 79:* 364.

PUCA,F.M., et al. (1971): Comparative estimation of psychological effects in parkinsonians with amantadine and L-dopa. *Acta Neurologica 26(6):* 707.

PURPURA,D.P., T.L.FRIGYESI, and A.MALLIANI (1967): In, YAHR, M.D., and D.P.PURPURA (Eds.): *Neurophysiological Basis of Normal and Abnormal Motor Activities*. New York: Raven Press.

RANSON,S.W., and S.L.CLARK (1959): *The Anatomy of the Nervous System*. 10th ed. Philadelphia: W.B.Saunders.

RANSON,S.W., S.W.RANSON,Jnr., and M.RANSON (1941): Fiber connections of corpus striatum as seen in Marchi preparations. *Arch. Neurol. Psychiat. (Chic.) 46:* 230.

RHINES,R., and H.W.MAGOUN (1946): Brain stem facilitation of cortical motor response. *J. Neurophysiol. 9:* 219.

RIECHERT,T. (1964): In: SCHALTENBRAND, C.T., and C.N. WOOLSEY (Eds.): *Cerebral Localization and Organization*. Madison: Univ. Wisconsin Press.

RIGRODSKY,S., and E.B.MORRISON (1970): *J. Amer. Ger. Soc. 18:* 142.

RIKLAN,M. (1973): *L-dopa and Parkinsonism: A Psychological Assessment*. Springfield, Illinois: Chas.C.Thomas.

RIKLAN,M., L.DILLAR, H.WEINER, and I.S.COOPER (1960): Psychological studies on effects of chemosurgery of the basal ganglia in parkinsonism. 1. Intellectual functioning. *Arch. Gen. Psychiat. (Chicago) 2:* 22.

RIKLAN,M., and E.LEVITA (1969): *Subcortical Correlates of Human Behaviour. A psychological study of thalamic and basal ganglia surgery.* Baltimore: Williams and Wilkins.

RINVIK,E. (1966): The corticorubral projection in the cat. Further observations. *Exp. Neurol. 12:* 278.

ROBINS,R.H. (1971): The structure of language. In MINNIS,N. (Ed.): *Linguistics at Large.* London: Victor Gollancz.

ROCHFORD,G., and M.WILLIAMS (1965): Studies in the development and breakdown of the use of names. Part IV. The effects of word frequency. *J. Neurol. Neurosurg. Psychiat. 28:* 407.

ROSE,S. (1970): *The chemistry of Life.* Pelican original. Penguin Books.

SAUSSURE,F.de (1916): *Cours de Linguistiques Générale.* Paris: Payot.

SCHALTENBRAND,G. (1965): The effects of stereotactic electrical stimulation in the depth of the brain. *Brain 88:* 835.

SCHILLING,R. (1925): Experimentell-phonetische Unterschungen bei Erkrankungen des extrapyramidalen Systems. *Archiv. für Psychiatrie und Nervenkrankheiten 75:* 419. Cited by Crewel, 1957.

SCHLESINGER,E.B. (1954): Surgical therapy. In DOSHAY,L.J. (Ed.): *Parkinsonism and Its Treatment.* Philadelphia: J.P.Lippincott.

SCHWAB,R.S. (1968): Limitations in treatment of Parkinson's disease. *New England J. Med.* 279(1): 943.

SCHWAB,R.S., A.C.ENGLAND, and E.PETERSON (1959): Akinesia in Parkinson's disease. *Neurology* 9: 65.

SELBY,G. (1967): Stereotactic surgery for the relief of Parkinson's disease. II. An analysis of the results of a series of 303 patients (413 operations). *J. neurol. Sci. 5:* 343.

SHARMAN,D.F., L.J.POIRIER, G.F.MURPHY, and T.L.SOURKES (1967): Homovanillic acid and dihyrdroxyphenylacetic acid in the striatum of monkeys with brain lesions. *Canad. J. Physiol. Pharmacol. 45:* 45.

SHERRINGTON,D.C. (1897) (with M.FOSTER): *The Central Nervous System* Vol. 3 in M.FOSTER: *A Text Book of Physiology,* 7th ed. London.

SIEGEL,S. (1956): *Nonparametric Statistics for the Behavioural Sciences.* International Student Edition. New York etc.: McGraw Hill.

SMITH,M.C. (1967): Stereotactic operations for Parkinson's disease: anatomical observations. In D.Williams (Ed.): *Modern Trends in Neurology 4:* 21.

SNEDECOR,G.W., and W.G.COCHRAN (1967): *Statistical Methods.* 6th ed. Iowa State University Press.

SOUQUES,A.A. (1908): Palilalia. *Revue Neurol.* (Paris) p.340.

SOUQUES,A.A. (1921): Rapport sur les syndromes parkinsoniens. *Rev. Neurol.* (Paris) 28: 534.

SPIEGEL,E.A. (1964): Physiology of the striopallidum in relation to extrapyramidal function and disorders. In TRABUCCHI,E., R.PAOLETTI, and N.CANAL (Eds.): *Biochemical and Neurophysiological Correlations of Centrally Acting Drugs.* Oxford, London, etc.: Pergamon Press.

SPIEGEL,E.A., and E.G.SZEKELY (1961): Prolonged stimulation of the head of the caudate nucleus. A.M.A. *Arch. Neurol. 4:* 55.

SPIEGEL,E.A., and H.T.WYCIS (1962): *Stereoencephalotomy.* Part II. New York: Grune and Stratton.

SPIEGEL,E.A., C.ZANES, and H.T.WYCIS (1965): Treatment of parkinsonian speech disturbances refractory to stereotactic procedures. *Confin. neurol. 26:* 458.

STEG,G. (1964): α-Rigidity in reserpined rats. *Experemtia 20:* 79.

STEG,G. (1969): Striatal cell activity during systemic administration of monoaminergic and cholinergic drugs. In GILLINGHAM,F.J., and I.M.L.DONALDSON (Eds.): *Third Symposium on Parkinson's Disease.* Edinburgh and London: E. & S.Livingstone.

SVENNILSON,E., A.TORVIK, R.LOWE, and L.LEKSELL (1960): Treatment of parkinsonism by stereotactic thermo-lesions in the pallidal region. *Acta psychiat. Scand. 35:* 358

SZABO,J. (1962): Topical distribution of the striatal efferents in the monkey. *Exp. Neurol. 5:* 21.

THORNDIKE,E.L., and I.LORGE (1944): *The Teacher's Word Book of 30,000 Words.* New York: Columbia University.

TILLEARD-COLE,R.R., and J.MARKS (n.d.): *Scientific Aspects of Psychological Medicine.* London: Roche.

TRETIAKOFF,C. (1919): *Contribution à l'étude de l'anatomie pathologique du locus niger de Soemmering avec quelques déductions relatives à la patholgenie des troubles du tonus musculaire et de la maladie de Parkinson.* Thèse, Paris. No. 293.

TWAROG,B.M., and I.H.PAGE (1953): Serotonin content of some mammalian tissues and urine and a method for its determination. *Amer. J. Physiol. 175:* 157.

UDENFRIEND,S., B.WITKOP, B.G.REDFIELD, and H.WEISSBACH (1958): Studies with reversible inhibition of monoamine oxidase: Harmaline and related compounds. *Biochem. Pharmacol. 1:* 160.

VAN BUREN,J.M. (1963): Confusion and disturbance of speech from stimulation in vicinity of the head of the caudate nusleus. *J. Neurosurg. 20:* 148.

VAN BUREN,J.M., and R.C.BORKE (1969): Alterations in speech and the pulvinar. *Brain 92:* 255.

VERNET,J.P., et al. (1973): Study of the evolution of intellectual potential and of memory in parkinsonians treated by L-dopa. *Annales Medico-Psychologiques 1(3):* 413.

VOGT,M. (1954): The concentration of sympathin in different parts of the central nervous system under normal conditions and after the administration of drugs. *J. Physiol. 123:* 451.

VON ECONOMO,C. (1917): Encephalitis lethargica. *Wien. Klin. Woch. 30:* 581.

VONEIDA,T.J. (1960): An experimental study of the course and destination of fibers arising in the head of the caudate nucleus in the cat and monkey. *J. comp. Neurol. 115:* 75.

WALBERG,F. (1956): Descending connections to the inferior olive. An experimental study in the cat. *J. comp. Neurol. 104:* 77.

WALSHE,F.M.R. (1948): On the role of the pyramidal system in willed movements. *Brain 70:* 329.

WALSHE,F.M.R. (1955): A clinical analysis of the paralysis agitans syndrome. In CRITCHLEY,M. (Ed.): *James Parkinson (1755-1825): a bicentenary colume of papers dealing with Parkinson's disease, incorporating the original 'Essay on the Shaking Palsy'.* London: Macmillan.

WALTZ,J.M., M.RIKLAN, S.STELLAR, and I.S.COOPER (1966): Cryothalamectomy for Parkinson's disease: A statistical analysis. *Neurology (Minneap.) 16:* 994.

WATKINS,E.S., and D.R.OPPENHEIMER (1962): Mental disturbances after thalamolysis. *J. Neurol. Neurosurg. Psychiat. 25:* 243.

WEBSTER,K.E. (1961): Cortico-striate interrelations in the albino rat. *J. Anat. (Lond.) 95:* 532.

WEBSTER,K.E. (1965): The cortico-striatal projection in the cat. *J. Anat. (Lond.) 99:* 329.

WILSON,S.A.K. (1925): Some disorders of motility and of muscle tone, with special reference to the corpus striatum. *Lancet 2:* 1-10, and 53-62.

WILSON,S.A.K. (1954): *Neurology*. Vol. 11. 2nd ed. London: Butterworth.

WINGFIELD,A. (1966): *The Identification and Naming of Objects*. Unpublished D. Phil. thesis, Oxford University.

WOOLLEY,D.W., and E.SHAW (1954): A biochemical and pharmacological suggestion about certain mental disorders. *Science 119:* 587.

YORK,D.H. (1967): The inhibitory action of dopamine on neurones of the caudate nucleus. *Brain Res. 5:* 263.

YORK,D.H. (1968): A microinontophoretic study of neurones in the globus pallidus - putamen complex. *Aust. J. Exp. Biol. Med. Sci. 46:* 3.

YORK,D.H. (1970): Possible dopaminergic pathway from substantia nigra to putamen. *Brain Res. 20:* 233.

ZIMMERMAN,J.D., et al. (1959): *Speech therapy for Parkinsonian patients after brain surgery. Immediate and long-term goals.* Paper read before the 35th Annual Convention of the American Speech and Hearing Association. Cited in Canter, 1961.

# APPENDIX

MAWDSLEY, C., and C.V.GAMSU (1971); Periodicity of speech in Parkinsonism. *Nature, Vol.231, No.5301,315-316.*

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# Periodicity of Speech in Parkinsonism

IMPAIRMENT of speech, leading sometimes to unintelligibility, was recognized by Parkinson[1] to be part of the disease which now bears his name. Reduced voice volume, dysarthria and prosodic monotony are common manifestations of Parkinsonism[2] and are generally attributed to hypokinesis, a cardinal feature of the disease, the physiological basis of which is ill understood. The term itself is difficult of definition, but it is generally thought to imply a delay in initiation of movement combined with slowness and restriction in amplitude of movements once initiated.

Quantitative assessment of hypokinesis is difficult but an objective analysis of speech function offers a basis for investigation. Joshua Steele[3] emphasized the importance of pauses in the rhythm of speech. Little study has been made of the relationship of sounds to pauses in the speech of Parkinsonian patients. L-Dopa in large oral doses has been shown by many investigators to ameliorate Parkinsonism and particularly to improve the hypokinetic defects thereof. We have studied the periodicity of phonation and pauses in patients suffering from Parkinsonism and the alterations produced in these parameters by treatment with L-dopa.

Twenty Parkinsonian patients, aged between 41 and 76, were investigated. Sixteen suffered from the idiopathic disease, paralysis agitans, and two of these had earlier been treated by bilateral stereotactic thalamotomies. The remaining four patients suffered from the post-encephalitic form of Parkinsonism. All derived perceptible benefit from treatment with L-dopa as gauged by their general functional capacity and mobility[4]. This was the only criterion for inclusion. Patients were not selected because of the nature of their speech defect, nor because of a specifically noteworthy improvement in speech function. They were all observed in hospital during the period of treatment. Recordings of their speech were made before treatment was instituted, and again when clinically they were adjudged to have improved, usually after taking L-dopa for 3 or 4 weeks.

Extensive studies of spontaneous speech and reading were made at each recording session after an introductory conversation designed to minimize the inhibitions attendant on the test situation. During each session the patient was asked to count from one to ten, with no instructions about loudness or the rate of utterance required. We thought that counting to ten would be the most apposite test for a study of speech periodicity. It is a universally familiar activity with constituents which are, with one exception, monosyllabic. In the act of counting there are no constraints on the rhythms of speech determined by

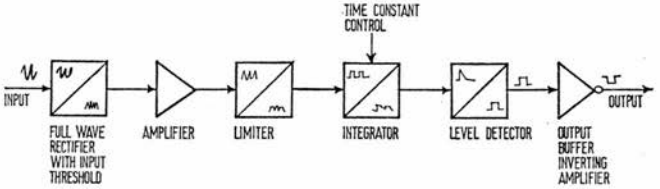


**Fig. 1** Diagram of signal detector.

punctuation delays. Counting conforms to Hughlings Jackson's[5] "automatic" utterance. It is, therefore, virtually free of those hesitations consequent on the formulation of "superior" or propositional speech which have been extensively studied by Goldman Eisler[6].

The recordings were played through a signal detector which was triggered by sound (Fig. 1). For accurate measurements of phonations this apparatus required that the patient's speech should be at least 20 dB louder than the background noise level. This provided a signal of 10 V, the input threshold of the detector being 1 V. In practice these conditions were achieved.

The initial delay to production of the first digit was not assessed. The phonation times for each of the ten digits and the duration of each of the nine intervening pauses were measured. When, as occasionally occurred, two phonations ran together without detectable pause, the total phonation time was halved and this value was allotted to each digit. Means and standard deviations for the duration of each phonation and each pause were calculated for each patient before treatment was started and again while on L-dopa, and the results are shown in Table 1.

These data show that the mean phonation time for single digits decreased significantly ($P < 0.01$) after treatment ($339 \pm 85$ ms) compared with the pretreatment figure ($389 \pm 107$ ms). In addition the variability of the phonations was reduced. Before treatment the standard deviations of individual patients give a mean value for the group of $139 \pm 55$ ms. After treatment the corresponding figure is $108 \pm 36$ ms. The change is significant at the 1% level. After treatment the mean duration of each pause ($440 \pm 227$ ms) was longer than the mean in untreated patients ($372 \pm 194$). This difference, however, is significant at only the 10% level of confidence.

Six patients, 2, 5, 13 and 20, who had suffered from the post-encephalitic form of Parkinsonism and 8 and 19 who had earlier undergone bilateral thalamotomies, were assessed clinically as showing little or no improvement in their speech after treatment with L-dopa. If they are subtracted from the group then the lengthening of the duration of pauses in the remainder becomes significant at the 1% level. There is too an apparent narrowing of the variation of the pause durations. Before treatment the mean of the standard deviations for the

**Table 1** Duration of Phonation of Parkinsonian Patients before and after Treatment with L-dopa

| Patient No. | Duration of phonations (ms) | | Duration of pauses (ms) | |
|---|---|---|---|---|
| | Before treatment Mean s.d. | After treatment Mean s.d. | Before treatment Mean s.d. | After treatment Mean s.d. |
| 1 | 689±199 | 522±125 | 382±149 | 638±80 |
| 2 | 398±153 | 260±126 | 569±157 | 480±142 |
| 3 | 428±104 | 408±95 | 430±114 | 411±108 |
| 4 | 245±142 | 230±103 | 138±74 | 394±68 |
| 5 | 415±142 | 405±95 | 172±100 | 152±78 |
| 6 | 314±106 | 404±126 | 640±144 | 827±192 |
| 7 | 305±87 | 322±70 | 650±142 | 750±150 |
| 8 | 302±116 | 242±56 | 470±195 | 203±50 |
| 9 | 366±115 | 283±101 | 520±90 | 688±70 |
| 10 | 320±112 | 261±132 | 705±133 | 493±113 |
| 11 | 464±82 | 255±61 | 328±181 | 504±114 |
| 12 | 315±123 | 285±98 | 617±332 | 722±184 |
| 13 | 285±128 | 286±106 | 302±138 | 155±45 |
| 14 | 385±110 | 330±120 | 265±128 | 330±149 |
| 15 | 368±199 | 350±110 | 216±72 | 205±93 |
| 16 | 588±182 | 473±71 | 355±138 | 708±118 |
| 17 | 366±168 | 336±93 | 101±36 | 365±154 |
| 18 | 496±85 | 483±118 | 158±75 | 211±100 |
| 19 | 415±321 | 350±222 | 132±97 | 86±33 |
| 20 | 320±106 | 302±139 | 288±72 | 475±84 |
| Group | 389±107 | 339±85 | 372±194 | 440±227 |

whole group of twenty patients is 128±62 ms; after treatment 106±44 ms. However, this apparent change does not achieve significance at the 10% level of confidence.

Estimates of the rates of speech during counting can be derived from these results. In patients before treatment the mean rate was eighty-nine words per minute, and after treatment eighty-eight words per minute. These figures are surprisingly similar to the average rate of eighty-seven words per minute which we found in twenty subjects, matched for age, who suffered from no neurological lesion and who were asked to count from one to ten in similar conditions to the Parkinsonian patients.

The speech of most of the patients in this group became more intelligible after treatment with L-dopa. Improvement in voice volume and in dysarthria contributed to this, but the changes in periodicity shown above are also important. The rate of speech does not alter, but each digit takes a significantly shorter time for its utterance and is separated from its preceding and following numbers by lengthened pauses. There is too a tendency for both phonations and pauses to be more regularly distributed after treatment. Shorter, crisper sounds separated by better defined pauses would be expected to improve the

clarity of speech, and so they do. These results are compatible with the observations of others[7] about the improvement of speech function in Parkinsonian patients treated with L-dopa. They indicate that this improvement is particularly manifest in patients with paralysis agitans. There is a suggestion, which needs further study, that in those patients with the post-encephalitic disease and in those who have undergone stereotactic thalamotomy, L-dopa may be less effective in improving speech.

The concept of motor deficit in Parkinsonism as a simple slowing and paucity of movements is inadequate to explain these observed changes in speech periodicity. The more rapid phonations are explicable on the basis of rectification of hypokinesis; but the greater separation of phonations which our results suggest implies a process more complex than a mere speeding up of motor activity. Nor is this consideration peculiar to speech function. The gait of many Parkinsonians is rapid even though the individual steps be short. Indeed, some patients show a tendency to involuntary acceleration, or festination, of their gait. In such patients L-dopa often produces not a more rapid progress but a more controlled gait, longer steps being taken more slowly. As Denny-Brown[8] has pointed out, there is in Parkinsonism a defect in the general quality of motor performance.

It is interesting to speculate, in the light of recent biochemical and physiological findings on the underlying mechanisms of the speech disturbances and their amelioration by L-dopa. There is overwhelming evidence that a decrease in striatal dopamine is an almost invariable factor in the production of the Parkinsonian syndrome[9,10]. Dopamine applied microelectrophoretically leads to inhibition in many neurones in the caudate nucleus[11].

Mettler[12] has shown that bilateral lesions of the caudate nuclei in apes produce over-activity, or hyperkinesis, which is driven by proprioception impulses. The principal outflow from the striatum is to the pallidum which itself lies in the efferent pathway from the thalamus for movement evoked by proprioceptive impulses. Purpura *et al.*[13] have demonstrated that stimulation of the caudate inhibits the outflow of impulses from the pallidum. Mettler[14] concludes that the striatum normally inhibits the thalamopallidal circuits and hence allows the organism to make choices and not to be dominated by sensory, and particularly proprioceptive, stimuli.

Lenneberg[15] postulates that if delays are introduced into a feedback monitoring system for speech the cues for the beginning of the next cycle of activity are delayed and hence there is a prolongation of the ongoing motor activity. This leads to a drawing out of vowels.

We suggest that the principal lesion in Parkinsonism lies in the striatum, the malfunction of which releases the thalamopallidal circuit from inhibition and hence kinaesthetic inform-

ation from the speech organs is submerged in random proprioceptive impulses. The choice of the next pattern of motor activation is delayed because of this confusion of information which effectively leads to the prolongation of the ongoing phonation. Restoration of the inhibitory striatal action, by activation of dopaminergic neurones, restores a more rapid selection of the cues for the next stage of motor activation, thus shortening the phonation times for individual words and lengthening the pauses. This hypothesis ignores the effect of auditory feedback which would, of course, be normal in most Parkinsonian patients. It seems likely, however, that kinaesthetic impulses from the muscles of the speech organs function as a monitoring mechanism, additional to auditory feedback, for spoken speech. Such a theory fits the facts of our observed data.

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C. MAWDSLEY

*Department of Medical Neurology,*
*University of Edinburgh*

C. V. GAMSU

*MRC Speech and Communication Unit,*
*University of Edinburgh*

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[1] Parkinson, J., *An Essay on the Shaking Palsy* (Sherwood, Meely and Jones, London, 1817).
[2] Canter, G. J., thesis, Univ. Michigan (1961).
[3] Steele, J., *Prosodia Rationalis* (Nichols, London, 1779).
[4] Mawdsley, C., *Brit. Med. J.*, **1**, 331 (1970).
[5] Jackson, H. J., *Brain*, **1**, 304 (1878).
[6] Goldman Eisler, F., *Psycholinguistics* (Academic Press, London and New York, 1968).
[7] Rigrodsky, S., and Morrison, E. B., *J. Amer. Ger. Soc.*, **18**, 142 (1970).
[8] Denny-Brown, D. E., in *Diseases of the Basal Ganglia, Handbook of Clinical Neurology*, **6** (edit. by Vinken, P. J., and Bruyn, G. W.) (North-Holland, Amsterdam, 1968).
[9] Ehringer, H., and Hornykiewicz, O., *Klin. Wschr.*, **38**, 1236 (1960).
[10] Bernheimer, H., Birkmayer, W., and Hornykiewicz, O., *Klin. Wschr.*, **39**, 1056 (1961).
[11] Bloom, F. E., Costa, E., and Salmoiraghi, G. C., *J. Pharmacol. Exp. Therap.*, **150**, 244 (1965).
[12] Mettler, F. A., *J. Comp. Neurol.*, **83**, 93 (1945).
[13] Purpura, D. P., Frigyesi, T. L., and Malliani, A., in *Neurophysiological Basis of Normal and Abnormal Motor Activities* (edit. by Yahr, M. D., and Purpura, D. P.) (Raven Press, New York, 1967).
[14] Mettler, F. A., in *Neurophysiological Basis of Normal and Abnormal Motor Activities* (edit. by Yahr, M. D., and Purpura, D. P.) (Raven Press, New York, 1967).
[15] Lenneberg, E. H., *Biological Foundations of Language* (Wiley, New York, 1967).

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